Third Meeting of the
Secretary's Advisory Committee on Xenotransplantation

Transcript

Plenary Sessions

Thursday, November 29, 2001

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P R O C E E D I N G S
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Agenda Item: Opening Remarks

DR. VANDERPOOL: Let's begin our meeting. Being with all of you at this, our third meeting, carries a very special meaning for me as it may also for a number of you. At our first meeting we began to become acquainted with each other professionally and personally for a number of us to renew deep and past acquaintances.

I said at that time that we faced the challenge of a steep learning curve which we began to climb as at that first meeting we surveyed the many scientific, clinical, legal, philosophical, and ethical issues surrounding xenotransplantation by drawing upon the knowledge and expertise of our own SACX committee members, drawing upon the knowledge and wisdom of Dr. David Cooper, Dr. Hugh Auchincloss and others and upon the knowledge and experience of our ex officio members such as Dr. Louisa Chapman and Dr. Eda Bloom.

Then at our second meeting in July we focused on infectious disease issues and agreed to form two working groups that are to compose two reports: One, an up-to-date analysis of scientific and safety issues; and the other a thorough analysis of the many challenging and at points new and different issues pertaining to informed consent for prospective recipients of experimental xenotransplants.

While the events surrounding and following the traumatic and history-changing terrorist attacks on September 11 had the effect of delaying the organization and work of these groups, these events did not keep us from identifying the SACX participants and co-chairs of these groups. And thanks, always, to the work of our executive director, Dr. Mary Groesch, we also held two teleconferences that initiated the work of these groups and set the stage for the breakout sessions and progress reports that will be held during this meeting.

One other comment about these background and foreground remarks, while I cannot and would not assume to speak for you, my own commitment to the work of this committee has been deepened since September the 11th. To be sure, it is right and fitting to respond by fulfilling one's roles in one's respective work situation, but for me these events and my day-to-day emersion in the news has also led me to want to do more to seek to make some contribution at a national level. Perhaps my greatest opportunity to make such a contribution rests in the work and responsibilities of this SACX committee for which I am now all the more thankful and to which I am all the more committed. I hope and trust that a number of you share these feelings.

Now, this, our third meeting, encompasses an exciting agenda that includes reports of ex officio members, a lengthy special update session beginning at 10:45 today that includes reports from cutting-edge experts whom we shall soon hear from, breakout working group sessions and reports. And in keeping with the consensus we reached at our last meeting, special attention to learning and thinking about xenotransplantation clinical trials. This is in keeping with the second item of the committee's charter, the charter in which is found in our meeting materials which says that one of the committee's charges is to, quote, review current and proposed xenotransplantation clinical trials, identify and discuss the medical, scientific, ethical, legal, and socioeconomic issues raised by these clinical trials.

I feel strongly that the makeup of this committee will enable us to fulfill this mandate of our charter. As a footnote, please add to your materials the extra materials provided for us today to add under Tab 3.

Now, my final remarks, introductory remarks, is that having summarized some things about the past and the present, I want us to be thinking about the future, where we should go from here beginning with our forthcoming March 2002 meeting. We will, of course, want to continue the tradition of updates about new scientific developments, reports on national and international meetings and notable ethical and moral position papers. But as we continue our deliberations, let's be asking ourselves what would we like to focus on: The content and completion of the two reports of our working groups? Pressing issues relating to international guidelines and regulations? A critical review of appropriate surveillance modalities in light of previously established surveillance mechanisms? Attention to ways to augment and focus financial resources on xenotransplantation research? A return to infectious disease issues that includes concerns over possible legal liability?

I could comment, I think, on some of the history of such concerns, issues and questions related to the birth of the, the hope for the birth of the knockout pig, including the technology that is involved in producing them. I think we have the possible challenge of being ahead of the curve on that issue. Possibly a critical review of guidelines related to animal use and care. Ways to inform and educate the public as well as discover what is known and what should be known about public opinion and/or a review of up-to-date developments and alternatives to xenotransplantation.

In keeping with the rubric about, that we are hearing about the holiday season, I've given you my shopping list. And before the meeting ends I want to hear from you about your list so that we will be able to have a better indication of where we, as a group, want to go.

With no further comments at this point I will turn the mike over to our executive director, Dr. Mary Groesch, who will make some introductory remarks and then begin to introduce the speakers beginning with Dr. Eda Bloom. And then we'll take a break and beginning at 10:45 listen to and exchange thoughts and ideas and questions with our notable experts, Dr. Cooper, Dr. Fishman, Dr. Massicot-Fisher, Dr. Robin Pierson and, I will admit, yours truly. But that should be an exciting session.

And then later this afternoon we will focus on our working groups and introduce the topics of these groups and go into the breakout sessions and come back and report and ask questions about this. Our two groups are working separately, but one of our challenges is to remain informed as full committee about what the other group may be doing. So, Mary.

DR. GROESCH: Thank you, Harold. And I don't really have any other announcements. I'm just glad that everybody could make it and appreciate the people who were able to make it here in the audience. I know it was quite a trek for many of you, so we appreciate it.

Today's first presentation is on the Pilot U.S. National Xenotransplantation Database. First we'll have remarks from Eda Bloom talking about the concept of the database and then a demonstration. And Dr. Bloom is chief of the Laboratory of Immunology and Virology within the Division of Cellular and Gene Therapies. She is also chair of the Xenotransplantation Action Plan. She is with the Center for Biologics Evaluation and Research, known as CBER, with the FDA. And then the demonstration will be by Mr. Tom Kruthers and he's with TRW and Stellar Systems under contract to the FDA.

Agenda Item: Pilot U.S. National Xenotransplantation Database: Updates and Demonstration.

DR. BLOOM: Good morning. It's my pleasure to be here. The first thing that I would like to emphasize, as mentioned on the title slide, you must realize that our database at this time is still in pilot form, it's not functional. We are not collecting full sets of data at this time. However, we've spent a good amount of time planning it and we expect to implement in the foreseeable future.

I'm going to talk to you about general issues of repositories and databases and why such are useful for what we need. And then I'm going to get more specific about the National Xenotransplantation Database, or NXD as we call it. And finally, I'm going to give you probably more information than you want to hear about how we intend to use it.

In general why do we use databases for suppositories -- got that? "Good morning" -- repositories (whereupon laughter) for surveillance. Everybody is awake, that's good.

They improve the ability to maintain data centrally, to retain information over time far better than any means that we have had to do so in the past, and it can be accessed from multiple locations. And perhaps some subsequent speakers will tell you about potential for international types of surveillance. They enable quicker access to safety data, obviously the technology again, and can be used to support clinical research and safety surveillance. As far as surveillance, the database can impose linkages; that is, they can enable you to link different kinds of information in different kinds of subject areas. They facilitate the indexing of verbatim; that is, whatever text you choose to put in, and also using controlled vocabularies. They facilitate information

storage and retrieval, I guess I'm reiterating that point. And they can support data mining or long-term safety analysis using a proper data structure which turns data into information and analysis of information resulting thereby in knowledge.

The NXD itself was recognized as a need by public discussions over the last several years and other public input from scientific discussions and concerns as well as from international concerns. The NXD was first identified as a need publicly in a 1996 draft U.S. PHS guideline and is mentioned again in the 2001 version. The pilot was initiated in 1997 and the database is administered by FDA. Even though it's administered by FDA, however, a number of different agencies have been involved in its building and the database is built to serve the needs of all of these agencies, including CDC, NIH, HRSA, and the Office of the Assistant Secretary for Planning and Evaluation, OASPE.

The goals of this database in order to meet the needs of a variety of agencies are to facilitate the recognition of health events that may represent the outcomes of xenogeneic infections. It's to facilitate the linkage of these occurrences to common exposures on a national level; to support the notification of clinical centers and individuals regarding adverse events and to facilitate research assessments. Because of these goals you will see shortly that there is a variety of different types of information that the database will collect.

There are a number of issues that had to be addressed in building this database or in building the structure for it, including protecting patient identity but still allowing the linkages to exposures, including providing information but still protecting patient confidentiality. Of course the database is only as good at recognizing health risks as we can make it based on our current human knowledge. And another issue that we had to address was how to collect data during post-marketing periods. I'll get to that shortly. It's not a great answer, but it's what we have.

How to maintain patient confidentiality and identity, which is a prime issue for us. We don't mention patients' names in the database. However, we do have facilities and points of contact. For example, that would be the sponsor and points of contact of the sponsor, the animal facility and points of contact at the animal facility, the clinical center and points of contact. We do include, of course and obviously, patient clinical information as well as product information and animal health events, but, again, no patients' names.

We include pointers to other information which will be kept at the clinical center and at sponsor locations so that we can, if the need arises, obtain patient identity, close contacts and full medical record information, and that's the purpose of having the points of contacts. In addition we have pointers to patient and animal biological samples so that if necessary in the need of a public health emergency, such samples can be retrieved and used appropriately.

Now, one other main purpose of the database is to make data available to the general public. However, the database will contain a great deal of confidential information so access to the NXD, raw information will be restricted to specific PHS people, although there will be reports that will be generated that will be publicly available.

As far as recognizing the health risks and the post-marketing data collection issues, the resolution that we have hit upon for recognizing the health risk is again the indexing of information using controlled vocabulary and that will be MedDRA and you'll see an example of that after I finish my introduction, and using computer-assisted coding software. Database will be designed to consider assessments for common or shared exposures.

As far as the post-marketing data collection, what that means is that after a xenotransplantation product has received FDA approval for marketing we still need to be able to collect information on it. The risk does not necessarily go away. However, the way that we collect information is based on our IND and pre-marketing regulations at the current time, and so FDA will be developing policy to ensure that post-market information will also be submitted to the database.

Again, the information to be contained in the database will be obtained from the IND, including product information, any adverse events, all of which must be submitted to the IND. The NXD will contain, again, confidential information that will not be publicly available but reports will be publicly available that do not contain confidential information.

I'm going to talk to you briefly about the kinds of information that the database will contain. It falls within seven categories of reports, including about the facility, patient, procedure, adverse events, follow-up, death, and animal health events. The structure of this database is to encompass these seven types of reports.

How is the part where you are going to get more information than you probably need to know or want to know, but I would like to summarize the types of data that will be collected in this database. In each report will be collecting the sponsor name, date, and type of report, so although that's listed under each one I'm not going to repeat it every time, and that is an important connection between the types of reports that we are going to be receiving. And a facility report contains all the contact information for the facility, its name, phone, address, a crosslink to the IND number that is being used by the facility.

The second report is a patient report. And in addition to the above, it will contain IND and clinical trial information, and the patient information will be contained as a code that will be developed by the sponsor clinical center. The sex, race, blood type and MHC type of the respective recipient. In addition it will contain initials, date of birth, place of birth and the mother's first name. These were developed as a means to be able to go back and eventually, if necessary, identify the patient through the sponsoring clinical trial.
The procedure report will contain various identification information about the procedure itself, including links to the patient. It will contain the investigator, location and the clinical diagnoses that the procedure the xenotransplantation product is being used for. It will contain specific information about the product itself and will also contain other types of therapies that the patient is receiving.

The adverse event report will contain identification information about the adverse event including, again, the types of things that are in the IND. Description and outcome of hospitalization or other relevant history, relevant diagnostic tests and lab data that have been done to work up the patient, including the dates, the suspected product that may be perhaps a cause for the adverse event or the pathogen, and information on the reporter who's submitting this data because in this kind of report you may have it actually being filled out and sent in by a clinical investigator rather than the sponsor.

As far as the patient follow-up information we intend to collect clinical exam locations and diagnosis in addition to the other basic information. Among these, this information, we will have the status of the implanted xenotransplantation product. Co-morbidity is the primary condition, of course, and other conditions or complications that may be noted upon follow-up and additional medications, therapies, or whatever else has gone on with the patient since the last follow-up visit, including and most particularly any hospitalizations since the last follow-up, and again reporter information.

Patient death reports will include the general types of information we have seen before but also add the date of death, whether an autopsy was performed, the results of the autopsy, if available, and death certificate information.

The animal health event report will contain the type of animal health event, including the source animal, whether it was a source animal, whether it was a sentinel animal, whether it was a herd health event.
The report identification information will include, in addition to the IND and source facility, the herd number, the animal number, the animal date of birth. In this way, if necessary, one can go back and trace the herd to other patients that may have received a product from that herd, the animal to other patients that may have received a product from that particular animal. The event date, location and description will also be included.

Now, how will we use all of this information? And again, you will have a demonstration shortly. But in general, browsing software has been developed or adapted for review of information along several paths. These paths include the investigational new drug or IND path, which is also the clinical trial path. You can access it through a patient. You can enter in through a patient code. You can access it for an adverse event. You can say, okay, I want to see how many patients have developed a particular type of pneumonia and access through that. You can also access through the animal health event path.

Navigation along these predetermined paths enable short-term assessment of common exposures and can be done very rapidly and very easily.

In addition, the database contains an ad hoc query tool which broadens the capability of the database for safety surveillance. And you will, again, have a demonstration of how this type of thing works. As far as the NXD version 2.0 which doesn't mean anything to you, I mean, we all have versions of whatever software we use, but this is the system that we intend to use to collect data. It will be available early in FY02 -- not FY02, early in 2002, which is winter of FY02.

However, before implementation of it, even when the software becomes available, we still need to write and publish a guidance so people know what they need to do in order to provide the data to us. This guidance has to go out in draft form. You've seen our drafts. They're followed by a comment period and revision according to whatever comments we receive. We also will need to obtain appropriate clearances by the participating agencies as well as other appropriate government organizations that we'll need to clear.

And that's my introduction, and I would like to then allow you to have a demonstration of the actual database itself. I'll point out before Tom Kruthers and Jim Foss come up here to actually do the demonstration for you, that the data that you will see are not real, they are dummy data so that, obviously, in a public meeting we are not going to be able to show you real data. We do have, by the way, in order to develop this database, we did receive some real data from a couple of sponsors who actually did volunteer to participate in this. But that's not the data you will be seeing. Thank you.

DR. GROESCH: If there's any questions for Eda while we are setting up the demonstration, go right ahead.

DR. SCHECKLER: Eda, the medical practice is going towards an electronic patient record. What you've described sounded like a complete patient record to me, all the things that you listed would be, I can't think of hardly anything that would not be in a patient record. Are you trying to make a provision for transfer of an electronic medical record directly into the database?

DR. BLOOM: We are not trying to make a provision for the whole record to go into the database, because although I would imagine that a lot of the information we're collecting will be obviously contained in the patient medical record, there's also the animal health events and so forth that won't be. However, we do hope that we can develop an electronic means for submission of data and that certainly would be facilitated if the information was already in a electronic format, I would imagine.

DR. VANDERPOOL: Eda, I have a question also. As you were talking, I was very impressed by such a thorough database, but I also had for part of the time you were speaking one of my other hats on, which is member of our institutional IRB. And I was thinking about, okay, we have a protocol that involves patients and we are responsible for protecting patient confidentiality. And maybe we need at some point to discuss a little more what assurances of confidentiality there would be. It strikes me that in keeping with what Bill just asked, that it wouldn't take a rocket scientist to figure out who the patients are in light of the data here.

The question then would be who has access, if that's the case, who has access to this space and if access is delimited by certain numbers of people, then I think confidentiality would, could be promised within an institutional framework. But if, let's say the news media had access to this database, then the IRB would have to say, we can't give you very many assurances of confidentiality. You see? Obviously you see the question by your smile.

DR. BLOOM: This is something that we've given a great deal of thought to and, in fact, only very specific PHS employees will have access to the database itself. And even those will need to sign all kinds of confidentiality agreements as well as not just applying to the patient but applying to the confidential material that's in there from the manufacturer and product issues because there is a lot of confidential information that's going to be in there.

What will be made public are overall reports that will be entirely, "sanitized" may be the word, I'm not sure, that will not contain anything that is confidential from the patient aspect or from the product aspect.

DR. SALOMON: Actually, I would say from a confidentiality point of view, Harold, if you really take that

issue seriously, the problem is not at the level of the database, the problem is at the level of your institution. Since if you do three or four pig transplants of such-and-such an organ tomorrow, using your example at your institution, you know, I don't think that we should be worrying about Eda guaranteeing your patient's confidentiality, but rather your staff and everyone else in the institution is going to know exactly what's going on.

DR. VANDERPOOL: That's an excellent point. And it relates to an issue that Keith Reemtsma raised years ago and that is when clinical trials resumed for xenotransplanted organs, this is going to be very newsworthy research, and so who has the responsibility of thinking through those issues, welcome to the group. I mean, we are going to need to spend some time probably on those issues of media accessibility and maybe even think about certain guidelines for institutions. I'm not sure we can control any of that, but certainly the patients need to be told forthrightly what media access would be or not be with respect to their own experimental treatments.

MS. SHAPIRO: Not only that, but I think HPPA is going to also pose real challenges for this, particularly if we are going to do stuff on stored samples. There are all sorts of the authorization requirements and confidentiality requirements that will make a nightmare out of this thing.

DR. BLOOM: That's a very good point. We actually were involved in the rewrite of the HPPA reg. And we actually had this in mind, so that -- I don't know what actually came out because I know it came out before the end of the last administration and it was called back for this administration.

MS. SHAPIRO: Some of us hope it will be called back again.

DR. BLOOM: But if it's not, I think this part should be covered because it would be requested by FDA for patient surveillance purposes. It's an enormously long document, so I can't tell you.

MS. SHAPIRO: Eight hundred pages or something, yeah.

MR. BERGER: Eda, since there have been clinical trials going on and this won't be in effect until the fall of next year, what's being done to gather information from those trials right now?

DR. BLOOM: What's being done to gather information from those trials is what's being done for other INDs and it's being done within the context of the FDA continuing review. We don't have an electronic database yet. We just have our usual review mechanisms, the review of our clinical people and our product people, which is actually a rather limited group of individuals so that an attempt is made to make sure that the proper people see all of the adverse events and all of the product information.

We also have continuing regular meetings of all of the different IND reviewers of xenotransplantation INDs that include the product reviewer and the pharm/tox reviewer, veterinarians, the clinical reviewer and we get together and discussion issues relevant to those INDs, so it's the old-fashioned way right now.

MR. BERGER: Will all that then be entered in the system and the data that you are requesting for this system, is it already being gathered so it can be entered in?

DR. BLOOM: Yes. Shall we -- was there another question or?

DR. LUBINIECKI: Given the importance of this database in storing information and generating reports in the future, have you created some provisions to verify the accuracy of the data entry and also verify the accuracy that the software is working properly?

DR. BLOOM: For the last point I'm going to defr any software questions to our experts. As far as verifying data, FDA very often will make inspections, visits to sponsors, visits to facilities to verify data. There's no plan at the current time to do this routinely on every bit of data that's entered, but it is an avenue that we do have.

DR. GROESCH: Okay. Shall we proceed with the demonstration and then there will be time afterwards if there are some other questions? So we have Mr. Jim Foss and Mr. Tom Kruthers.

MR. FOSS: Tom Kruthers is going to be doing most of the presentation this morning, but I did want to say a few words because demos can sometimes be very difficult to look at and understand what's going on, especially for a large system like this. Our goal is not to get you to fully understand the system and all its capabilities, rather we just want to give you a peek, of course remind you that it does exist. I know you've heard a lot about it.

I would like to emphasize just a couple of points that Eda made. This system is developed for a very specific purpose, to collect information on patients involved in xenotransplantation, and a lot of the follow-up information that will come in subsequent to the procedures. We also collect data on facilities, animals that were involved in the procedures, and they are all linked together in a very complex database.

We had a lot of help building the system from a lot of people in this room. Our users, as Eda mentioned, are from the FDA, NIH, HRSA and CDC. We've engineered a solution for them to get remote access into the system even though it's behind the FDA firewall. The major components of the software are actually twofold: One is to get the data into the system through a data entry module. Tom will be talking about that in just a second. The second area is a software that allows the user to look at the data and that's, of course, what most of our users will be involved in.

There's three ways to do that. We have a browser which allows you to look at information along predetermined paths, you can start with an IND or you can start with a list of all patients, for example.

Then we have queries and reports. Probably the best way to explain the difference between the two is reports are preformatted. It's a selected information. You can put in conditions in terms of the scope of what you want to retrieve, but it's preformatted.

Ad hoc gives the user more flexibility. He cannot only format the information the way he wants but he can select different data fields to query against. We have both custom software that we built as well as some off-the-shelf tools. The ad hoc query tool is Oracle Discover.

Tom will also give you a short demonstration of another tool we use, it's an autoencoder, not meant to work alone. Of course it needs to be reviewed by a medical person and approved, but it helps the coding against a very large vocabulary we use in MedDRA. And again, Eda mentioned the mock data. Don't look at the data itself but the presentation because I'm sure you'll see some funny facility names, for example. So with that, I'll let Tom start.

MR. KRUTHERS: I'm Tom Kruthers. Please excuse me if I sit down because if I have to stand up, talk and work a computer at the same time I'm going to ask for a really big raise and I don't think Jim wants to do that. Okay.

Beginning with data entry, as Jim mentioned, data entry is the means by which we can enter all kinds of data into the database, we enter here the reports from sponsors, information about the INDs, our internal and our external points of contact and the various code lists that support our application.

So starting out we'll take you to our submission ledger, and this is the form on which we record all the submission reports. I'll just -- although Dr. Bloom has reviewed these for you already, but you can see all the various report types that are entered here on this screen. They are entered here and they are also edited from here. So just to show you an example of just one of the reports, we'll just take you down to one of our adverse event reports. Let me scroll down here a little bit.

We'll open up that report. Here you see the entry form for the adverse event information. I think the information in this report has been reviewed, but just quickly here, you have the type of report, the report date, the date of the adverse event, detailed description of the adverse event, other relevant history, test data. There are lab tests related to this adverse event, you record that information here. Any suspected causes, be they pathogen product concomitant drug, can be recorded. And of course information about the person giving that report.

And as Jim mentioned, we'd like to just give you a short demo of one piece of this form and that's where we employ our autoencoder to index the narrative text. So at this time I'll go ahead and launch that and we'll do the adverse event description. Give it a minute to initialize and fire up.

MR. FOSS: What it's doing right now is it's actually loading MedDRA into memory so it can match the vocabulary.

MR. KRUTHERS: As you can see, this has pulled a narrative text from the description. This is a very short one. It could be very much longer. And of course this was kind of selected words that describe the adverse event and it's very brief. But we'll go ahead and code those. And you can see in the lower right-hand box the preferred terms from the MedDRA vocabulary that were solicited by this text. And as Jim mentioned, of course there's a human intervention here, a medical coding specialist, who can add, delete, go into the source, pick words that were not immediately recalled or you can delete terms there that may be erroneous and go ahead and code those.

At this time we'll go ahead and we'll save these to the database. And we have six records added. You see them listed here on our coding cap. At this point if the terms were received from the sponsor, we can indicate those. We can also indicate a type against these index terms and real briefly, that's a long list. It could be part of the description or it could be even a social condition. For instance, married or divorced are sometimes listed in these descriptions and you would want to label that as a social condition so you don't distinguish that as part of the reason for the adverse event.

And we also record whether the term is relevant or just contributing. And for purposes of this demonstration I will just make all of our terms relevant. And we'll go ahead and save that information. And return to our submission ledger. And return to our main menu.

Okay. Now, you've seen a brief glimpse of how information is entered in there. Now I would like to go ahead and take you into the browser. As mentioned before, we have four primary paths to browse the information. And the names of these paths generally reflect the type of information that you are starting with as you go in to begin browsing.

Now, for purposes of this demonstration we will go ahead and start with the adverse event and we'll start with the adverse event that we just entered and here you see a list of all the adverse event reports across all INDs. And the event that we just entered or actually edited is the first one listed, highlighted in yellow, and without going through all the various tabs you can see there are all the same information that was entered. In this case we have a death report that was also entered, and the reporter.

Now, suppose, as an example, we would now like to view information about the patient involved in that adverse event, the procedures received by that patient and even the products used in the procedure and, beyond that, check and see if some of the same source animals in that product were used in other procedures. So that's an example of how one would begin to browse.

We have a button on the bottom lower left here which will take you to the patient demographic information for the patient involved in this particular adverse event. Now we have a glimpse of the patient and as mentioned what went into a patient report, you see sex, race, blood type, birth dates down to mother's first name. Death reports, if there had been one, and, of course, points of contact.

And as I mentioned, we wanted to say, okay, now that we've seen the patient, let's look at what procedures this patient has received. Again, I'm going to the button on the lower left, and now we see for that patient a listing of all procedures received by that patient. In this case he's had one procedure. Information associated with that off the procedure report, who the investigator was, facility, primary conditions, comorbidities, clinical indication. Here, again, these texts are also coded and you can see where the index terms are listed. And we mentioned any treatments received as part of this procedure are listed and recorded here.

And finally, let's talk a little bit about products since we wanted to track back to the product used in this

procedure. Here we only have one product listed for the demo. And if we want details about that product we can pull up a screen that tells what the biological source was, the product category and other information about the where and how of how that product was used. We can also, as part of our goal for our little browsing expedition here, we want to take a look at what source animals were used to make that product, and here we go off to a listing of all the animals that were used for that product. And information here, of course, is from the animal reports where we record the source facility, various points of contact, details about the animal, when it was born, product procurement date, species and strain of the animal.

And as we were going to find out, let's see if these animals were used in any other procedures. And here we go to a list of all the procedures that each of these animals were used in. In this case, as we scroll down, you can see all three animals were used in just that one procedure. And it could be, it could be many procedures and from there you could continue to track and browse.

So I think we will, at this point, go ahead back to our main menu screen and now that you've had a look at our browser and show you a little bit about the ad hoc queries. As Jim mentioned, this is an off-the-shelf product, Oracle Discover, and I've already got this launched here. But what we do is we build views of the database and Oracle Discover gives the user a window to these views where he can go ahead and develop and build his own personal queries.

In this case we'll go ahead and we'll open up our database. And we have several workbooks which are really files that represent queries from these views and we'll choose our, since we started with an adverse event, we'll continue with our adverse event theme here. And I will go ahead and launch one of these particular queries. And it will quickly run. And before we take a look at some of that data, let's go ahead and I'll bring up the edit sheet which shows you a little bit about how discovery is used.

On your left-hand screen you see basically the view and all the fields that are in that view. And with Discover you can select the particular fields that you want to use. In this particular case we picked fields that would identify the adverse event and the nature of that adverse event and information about the biological source that was used, and in this case the source facility name. And this would be useful in the case that we were just looking at that adverse event and if you just noticed, as we tracked through the browser, we reached the point where we were looking at the source animals and all the source animals came from the same source facility, a place called "Porcine Place" and now we could use this query to go ahead and say, okay, let's look at that facility, let's look at all the adverse events that were associated with animals from that facility and something about the nature of those adverse events.

And that's what we have here in this query. You can see our facility, Porcine Place. You see some of the coded terms that were associated with the adverse event from those animals from that source facility, and we actually have the hierarchy for these terms, the higher-level terms and system organ classes for those terms.

You can see the type of animals, species of train that was involved in the adverse event and you can see the adverse event that we entered here, the one on 8 September for that patient that resulted in hospitalization from an unknown pathogen. So it's really up to the user how he wants to develop, use and build these queries. They can be stored once they are done in his own personal file. He can run them and change them any time he wants and they can always be saved into an Excel spreadsheet where he can take it out and do whatever he wants with the information once hepulls it out of the database.

So at this point we'll go ahead and again return to our main menu. And we'll look at one final way to get information out of the database and that's through our preformatted reports. Here we have reports of basically two types. We have our submission reports, which are primarily quality assurance reports associated with checking data entry. These reports were previously described and what you have here is the database, can go ahead and reproduce those for, as I mentioned, quality assurance.

Now, we have a whole battery of analytic reports and what these do is they provide an aggregation of adverse event information across the entire database, by source facility, by product, by clinical center, even by MedDRA vocabulary term. And we'll just go ahead and use our example of Porcine Place facility and take a look at one of the reports. We'll just go ahead and use the source facility reports. In this particular case we have a report

selection screen.

Now, we've said these four reports are preformatted, but we've added a feature that allows the user to do a lot of the upfront criteria selection of what he wants in his report. In this particular case let's just say we are interested in adverse events and we are interested only in that particular facility, Porcine Place, so we'll add that report and go ahead and generate it. Now, excuse for the fact that the report doesn't quite fit the window, but you can see, I'll just kind of scroll from left to right here, you see we've got a report about Porcine Place, the herds in that facility, the animals in that facility, and as we track across, you can see the adverse events that were associated with that animal.

And here we have the 8 September report that we initially entered and edited. And in this particular case we were also showing the relevant adverse event preferred terms. If you remember way back when we edited that report we had the choice of putting relevant or contributing. In this case because I picked relevant for all of them, you see all of the same terms. So that's really only one report of many.

I'll just stay right here and you can have a little time for questions, but as Jim mentioned, this is a fairly large and complex database in terms of numbers of tables. And the NXD here has probably over 60 screens and over 20 reports. And it would take a lot more time than we have here today to go through all of it. But I hope from what you've seen you can appreciate the power of this tool in assisting and monitoring xenotransplantation recipients for adverse events, for coordinating public health response when that's required, and generally for just collecting useful information for the scientific community and public at large. So, at this point if there's something special you want to see or questions you want to ask, you are welcome to do it.

DR. GROESCH: Any questions for any of our speakers so far?

DR. KIELY: My question is pretty straight forward, it goes back to what you were talking about earlier with the data entry. And you take the reported language and convert it to this MedDRA?

MR. FOSS: Right.

DR. KIELY: Can you query from the reported language or once you do the MedDRA conversion that's --

MR. FOSS: No, actually that's one of the purposes of the indexing. The fields that store the narrative text are actually long fields and they're just a megabyte of data. It's just a phenomenal amount of text that you can put in there and the normal way that Oracle works, you cannot search on these long fields but you can search on the indexing terms. So that, if you wanted to, for example, do a query where you wanted to find information about adverse events where a particular term existed, you would want to use that index term and not the text, not search the text.

MR. KRUTHERS: But the verbatim text is still in the database, and on some of the browsers, let's say you were looking at a list of all INDs and you wanted to do a search, let's say of a particular word that might be in an IND title, you can do that and then just see those INDs that would come up reflecting that term you put in. So there are some fields you can do that.

DR. KIELY: My concern really was that at that point where that, it's, those specific -- it's left up to whoever is doing that to determine what would be relevant and if it's relevant as well as decide what -- and how many of those terms can you use per case?

MR. KRUTHERS: You mean how many terms can you associate --

DR. KIELY: In that exact example you had where you had --

MR. KRUTHERS: We had six. I don't know that there's any limit. You just keep adding terms and you can scroll down and see the terms. So to my knowledge, there's not any limit per se.

DR. KIELY: Because as a clinician what jumped out at me when you did this was that I saw "cough" appear

twice. That was felt to be relevant. Pneumonia, which was on the screen earlier, I didn't see what happened to pneumonia until the death report. I was just following the case as a clinician. And so it concerned me that potentially information that was reported could be changed.

DR. CHAPMAN: Could I just speak to that point? This may have been said earlier and I apologize if I just didn't hear it. But in case it wasn't, I think it's important that people understand that what MedDRA is, which is it's kind of equivalent to ICD-9 codes. It's a way of giving a standard, standardizing reports of medical illness, but this was developed for the regulatory industry. And I think the reason you didn't see pneumonia was just that all the spaces visible on the screen were full and it was on a lower space, I think you would have had to scan down for it. I don't think it disappears from the coding.

MR. FOSS: You are also bringing up a very good point about the software versus actually using the system. Because once you get into the area of medical coding of your reports to come in, you want a very standardized approach to that. I personally feel you should have that done specially by a few, small select group of people who understand the vocabulary and then apply those standards to how they are doing it so you have a common index across the table.

DR. VANDERPOOL: I have a question about the possibility of deep-sixing information you won't ever find again. Do you follow the Medline categories of illness and symptomatology so that if someone wanted -- and I saw "cough." Now, it seems to me that if you don't follow the Medline terminology or something like it, maybe that, then you could enter all kinds of information that would never come up because you are using terminology that's not standard and that could be sort of like putting a library book in a library that never will be found because it's somewhere on a shelf where it's not supposed to be.

MR. FOSS: Right. What you saw the indexing result in are the preferred terms from MedDRA. And that's what we store the, or index our data against. And I'm not an expert on MedDRA, but MedDRA does have hierarchies and I believe they did look at all, I tried to use ICD and so forth, when they built their vocabulary, and of course it's maintained continually. So you can go in -- maybe where you are going you can go in and do queries using some of the higher level terms and the hierarchies to group your data. What's actually stored is the preferred terms but the hierarchies of each preferred term are preserved in the database, so you then can query on the system organ class, for example, to retrieve.

DR. VANDERPOOL: It seems to me that if you really wanted to control these outlying terms that most people would not, never think to find or would guess around and maybe never uncover, that the entry, at the entry level when you wanted to submit a term, the database would have to tell you, no, you can't use that term, you need to use this term, or -- so that there would be a sort of forced standardization at the level of entry.

DR. SALOMON: I had a couple of questions, but one of them kind of follows nicely on what Harold was saying. One of the issues is going to be communicating and the use of words. For example, your concept of relevant event versus a contributing event, I respectfully submit that makes no sense to me at all as a clinician. And having spent a lot of time as a data safety officer I have no idea how to code something as relevant or contributing. That's not your problem, you are developing the database, so there's going to need to be a process is all I'm suggesting where you deal with real bedside experienced physicians and just, you know, so what would you do with "relevant," what would you do with that?

The second thing kind of falls logically, and that is exactly where is this data going to come from. If I follow this, I could see a couple of different things. Initially I thought you were talking about paper reports that then would get submitted to the FDA right now pretty much like how we handle a typical IND. Obviously everyone is going toward online data reporting yet these guys were talking about, quote, a medical coding specialist. I'm trying to figure out where an online data reporting system, a medical coding specialist would fit.

And then, lastly, we heard the concept a cadre of data entry people using a standard code which is another translation issue, not a bad suggestion by the way, just another place where words could get transposed and data lost.

DR. MICHAELS: Just to add to that. I actually think the question was more directed towards the accuracy of

the data entry level which then, because the more levels that we have trying to interpret what does it mean is something that we are going to have to think very hard about.

DR. BLOOM: First let me say that one of the first demonstrations that Tom showed you was a list of a few adverse event symptoms that were submitted. And then he did a manipulation, you saw a bunch of bars going across and those were converted to MedDRA terms, so the system will take terms that are not MedDRA and convert them, so that's where that happens rather than it being you as the reporter can only call this one thing, but the system will actually make a conversion for you.

The second issue about who is going to be doing the data entry and how that's going to be controlled and where the data are coming from. The data will initially be coming from what we already have in the IND so there will be retrospective data entered. Newly submitted data, I think, and I'm going to refer to Tina, I know she's here somewhere -- but I think it's going to be a choice that people can enter by paper, we can extract it from the IND or to make things easier there will be electronic data entry.

The difficulty with doing it on the web is security. But these are all things that we are entertaining and, in fact, trying to figure out how it can best be done. As far as the individual ascertaining of whether the data are correct, again, you know, a sponsor sends something to an IND now and they say this patient experienced pneumonia and there was an infection that was due to some kind of an organism, we have no way of checking the veracity of that. Did they enter the correct data into the database? It's going to be the responsibility of the people who actually do the entering to make sure they entered it correctly, but we can't, short of an inspection, check the veracity of the data that have been submitted.

DR. MICHAELS: Will you have a double entry to make sure that the two entries coincide?

MR. FOSS: Our policies will provide not only for QA of data entry but also for some of these reports you've got to enter the IND clinical trial and patient ID. And if that data isn't in there, it's going to, of course, flag the process and we would have to go back and look at the data.

I would also just like to mention the software that we have developed can easily be transcribed into a web site for data entry by individual sponsors. But that's more policy issue than software. Actually the way Oracle works, that can be done very easily. So we can provide additional capability down the road, if that's the decision, once the security and so forth.

DR. VANDERPOOL: We are going to have to move on to other issues. I'm going to use the authority of the chair to make one observation. If either wants to reply to, certainly do so. But again, the looming issue from, as we've already asked some very important scientific and questions involving accuracy of the data. But the looming ethical issue is, remains confidentiality as Mr. Kruthers presented the demonstration, we had as ad hoc queries that you could ask about sex, blood type, race, birth date, patient code, sponsor, clinical trial site, and then mentioned at the end, all of this information would be useful for monitoring and, quote, for the public at large.

So, again, the question is: Who gets entry to this base? Because it seems to me once you enter into the database, once you are able to get in, one can compromise confidentiality in rather profound ways. But that's an issue we'll have to wrestle with another time.

MS. SHAPIRO: Can I ask just one question on this data thing? Is it only going to include data from this country?

DR. BLOOM: Yes. The public will not have access to this database.

MS. SHAPIRO: Right. I'm just looking at the utility of this database and the informed consent process, and if we included everything we knew, it would be more helpful in the informed consent process. But it won't, it will just include this country.

DR. BLOOM: But the informed consent can include things that are going on in other countries, too. The

database will only consist of procedures that are performed in this country.

MS. SHAPIRO: There are bunches of purposes of this, I would think, and one is so that we have a repository of thorough information.

DR. BLOOM: Right. And there have been discussions at international levels about an international database. That's down the line, but those discussions have begun.

DR. SALOMON: I know we want to move forward and so I'm going to say can we later come back to something I would like to talk about, which is adverse event and serious adverse event reporting, because the question I would like to get some discussion on is whether or not our definitions of these and the current FDA rules for AE and SAE reporting is necessarily good for something like this in a prospective database.

DR. GROESCH: Okay. Let's move on. Our next presentation is an update on a centralized xenotransplantation biological archive. Our speaker is Dr. Louisa Chapman from the CDC. She is assistant to the director for Biologic Therapeutics within the Office of the Director, Division of AIDS, STD and TB Laboratory Research, and that's within the National Center for Infectious Diseases.

Louisa.

Agenda Item: Centralized Xenotransplantation Biological Archive: Update and Discussion.

DR. CHAPMAN: Thanks, Mary. First, a little background. The argument for a, or the reason for developing an archive of biological materials associated with source animals and xenotransplantation recipients is basically as a public safety insurance policy. In the best of all possible worlds, the expectation is that these samples will be archived and will never be accessed or used until the abolishment of the archive. But the reason for having them and the reason for investing that cost and effort is if a question arises about an unexplained illness that might be xenogeneic in origin or a cluster of unexplained illnesses that possibly are associated with or are clearly epidemiologically linked through analysis of the database with xenotransplantation procedures.

And with an archive like this, we'll have biologic specimens that you can go back and do laboratory investigations and have a reasonable possibility of identifying the etiology and the source of introduction of the infection. In the absence of such archives of biologic material, your probability of being able to successfully do that kind of investigation is very, very low.

In the 1996 draft guideline, responsibility for developing and maintaining these archives was assigned to the sponsor or perhaps to a number of individuals, the principal investigator, the laboratory animal facility and so on. The public comment received in response to that draft emphasized by multiple groups the perceived need for some sort of central public archive if in truth we thought it was important to develop and maintain these kind of archives.

This is the language paraphrased from the 2001 released revised guideline, which I'm sure you are all intimately familiar with by now, but just in case you overlooked this point, in Section 52 we talk about biologic specimen archives and the key language is saying, "The sponsor should ensure that the designated PHS specimens from the source animal, the xenotransplantation products and the recipients are archived, and those are addressed in sections 371, 353 and 412. For subsequent public health purposes including public health investigations if they become necessary."

And then there's further language that states that "DHHS is considering options for a central biologic archive by which was meant designated public health service specimens would be deposited in such central archive."

Now, just to review the specifics of what was talked about, Section 371 talks about what specimens from source animals and basically it talks about banking specimens at the time xenogeneic tissue for xenotransplantation product is procured and archiving it for 50 years from the date of the procedure, of the xenotransplantation procedure. And it gives examples, although all these examples are accompanied by the caveat that it may be appropriate to differ from what's outlined in the guideline and the basic requirement is that the sponsor needs to

justify the proposal for what sorts of materials are obtained in what amounts.

But ideally they talk about, minimally about ten half cc aliquots of plasma, and minimally about 5 aliquots of viable one times ten-to-the-seven leukocytes and at the time of necropsy tissue samples representative of all major organ systems, particularly those relevant to the material procured for the xenotransplantation product.

Section 412 talks about the recipients and it describes collecting at least twice prior to the procedure and after the procedure at roughly the following immediately, one in six months, one in two years and then five years for the life of the recipient, again collecting minimally three to five half cc aliquots of plasma and minimally two aliquots of one times ten-to-the-seven leukocytes. At the time of autopsy biopsy of the xenotransplantation product and all organ systems relevant either to the xenotransplantation procedure or thedeath of the recipient.

Section 353 talks about archiving at the time of procurement of biopsy of the xenotransplantation product itself or if that is likely to compromise the viability of the product of relevant tissue at the time of procurement, and I've taken a little liberty here, there are actually different sections of the guideline, but it also specifies that if the xenotransplantation product is rejected or removed prior to the death of the recipient, at that time a portion of product should be archived. So we are talking about a good number of specimens.

Now, I'd hoped to be able to give you something more definitive, but we are going to have to talk in very preliminary terms today because I have not been able to get some basic approvals that we need before we can go forward, but basically CDC has accepted responsibility for developing such a specimen archive, and our preliminary proposal is going to be that we develop it as a project under the CDC and ATSTR specimen packaging inventory and repository, which goes by the name acronym CASPIR.

The current status of this preliminary proposal is that it's on the drawing board because the first step in proceeding with that is approval of the CASPIR board and the CASPIR board meeting has been delayed due to other priorities of the agency.

A little background on CASPIR, basically CDC, because of the nature of our work, we receive specimens for many, many reasons and often this results in large specimen collections that are irreplaceable and therefore invaluable.

Those specimens historically were maintained by individual principal investigators -- no specimens at CDC belong to individual investigators, they belong to the branch or the office in which the investigator works, but they were maintained by individual sections or branches and there were times when large serum collections would have to be discarded because it wasn't financially feasible to retain them, there wasn't room for additional freezers or were lost because of freezer failures.

This is significant for our agency because there are a lot of times when collections of serum, for example, that were collected for one purpose later become invaluable in determining what's going on with another unexpected purpose. And one example is that there were large collections of serum that were collected for hepatitis C studies in the '60s and the '70s that turned out to be invaluable sources of information on the early epidemiology of AIDS when it was lymphadenopathy syndrome and nobody quite knew what it was except that it seemed to be something -- well, actually they weren't valuable until we knew it was associated with HIV and we had serologic screening, but at that point these were a lot of the early sources of information about AIDS.

At any rate, in response to this the agency made the decision to develop and fund centrally a large specimen collection archive which is CASPIR. It's a state-of-the-art facility which is owned by CDC. It has a guard force, it's monitored 24 hours a day, 365 days a year and for projects or collections to be deposited in CASPIR, the deposition has to be approved by a board, the CASPIR board, which has sort of administrative oversight of the project and that board also can and is responsible for periodically reviewing the collection and making recommendations about removal or discarding of collections.

It's contractor operated and it's been in operation since 1999. So what our preliminary proposal is, is to develop the, what for lack of a better name I'm calling the National Xenotransplantation Biologic Specimen Archive or NXBSA as a project under CASPIR, but I think from what I've already said, you probably already understand

that the first step in doing this is presenting it to the CASPIR board and gaining their approval, which hasn't happened yet.

The preliminary proposal that we've developed would establish within this project one collection for each xenotransplantation procedure that occurs. And we are proposing that the CDC-funded archive will maintain and will accept up to 250 specimens per collection. And if you remember, this is part of why I went through the details about what the guidelines suggests about guidance on specimen collections. 250 was picked because that's about the number you have if you get exactly what's outlined as ideal on the source animal, the recipient and make allowances for some necropsy and autopsy specimens.

The proposal that we've developed is a proposal whereby the project at CASPIR would receive, store and release when appropriate properly packaged specimens. There will be no processing done by the facility, so sponsors will be provided with information on proper packaging. If specimens arrive and they are not properly packaged, they will be returned. And the administrative custodian will be the director of DASTLR, Division of AIDS, STD, TB Laboratory Research, which is basically the office out of which I operate, NCID, CDC, or his or her designee.

What has to happen before we can make this, develop an operational system? Well, the first barrier is we have to get the approval of the CASPIR board. There's no precedent for this sort of storage actually. CASPIR was developed to store CDC collections for internal CDC use, it was not developed to store external collections. And since this is really a collection that will be developing and holding on behalf of the public health service, it's a little different from any precedent previously set. We don't honestly think this is going to be a problem, but we are asking, we will be asking permission to establish a project that's a little different from the purpose for which CASPIR was established.

There's the cost option. When the CDC accepted this responsibility, we didn't get any increase in funding from Congress to accompany it. And so we are looking at ways to defray that cost and this is something that obviously you could imagine could grow considerably over time, particularly if there was a successful clinical application that suddenly was enrolling a large number of people. So one of the things we are looking into is the feasibility, the possibility, the desirability of a user-fee system. That's not always a winning option for government agencies because sometimes Congress looks at the user fees and says, oh, you are getting that income, well, we can deduct it from your usual allocation, but we are investigating whether that would be a desirable approach.

One of the issues that is going to have to be resolved is who owns these specimens. Obviously if they're being sent in and deposited for the use of public health, the intent is they just remain there until they're needed for public health investigations. The intent is not that we store them until the investigator says, oh, I've come up with this pressing scientific issue and I want my specimens back. And, again, I'm having some discussions with the lawyers. We are going to have to develop, explore what the options are for defining ownership and probably develop some legal papers around that.

The convention for CASPIR is that all the specimens are owned by CDC. What has not been addressed and what I will explore with them is whether they will permit co-ownership, owned by CDC and someone else. Whether that someone else would be other public health agencies or the sponsors who would then have a right if the archive was abolished, to request their specimens back, or -- there isn't a precedent on that and I don't know what the outcome is going to be.

The other issue is going to be obviously informed consent. And many of the issues potentially -- many of the issues raised by the human genome project potentially may be raised here. Certainly there are issues that have come up in the past about use of specimens for things that eventually become profit producing for the person who develops the application. And, then, does the profit belong to the patient from whom the tissue came or to the person who had the intellectual ability to apply it. I think that's probably going to be fairly simple because that will probably be dealt with under ownership, and basically these can't be used for any profit-producing enterprises. But these are all issues that we have to work out that are actually going to probably be more time consuming and more difficult than actually developing the plan.

The time line I can't really tell you. I had hoped to come with a completed presentation now, but it's obviously going to be influenced by the decision of the CASPIR board and that's going to be influenced by when the CASPIR board meets. It was supposed to have met sometime in the last month and a half, but not only has it not met, I can't even get the person administering to respond to my e-mails asking when it will meet, and you-all can probably guess the reason for this is that all the high level people on the board and the administrator have been detailed to work on anthrax related problems, which we hope are on the decline.

Also, the thorniness of the legal, financial informed consent issues, which alternately seem more simple or more complex, I'm not sure how difficult or easy that is going to be to work out. And then the necessary agency priorities which that right now anything I -- my request for time or attention to this issue are not competing very strongly against agency priorities. But hopefully it will be operational no later than late 2002, maybe sooner, maybe not until 2003.

And the last pressing issue is that although NXBSA has that sort of Pogo ring, which is not inappropriate considering Pogo is in Okefenokee and the Okefenokee is in Georgia and this -- I'm open to suggestions if you've got a better name leading to a better acronym because you all know that acronyms are very important in governmental life.

Questions?

DR. SCHECKLER: There is no question that you pointed out that the CDC current archives are valuable. Another example is the Pontiac fever outbreak that occurred in July of 1968 and it wasn't until 1977 that it was found out to be legionella. And two years of dedicated work didn't answer the question until the laboratory data was available. I'm still skeptical about the 50-year time line, but I want to argue like I did in July about that.

What is the longest that the CDC has kept specimens that have been later found to be useful? And do you have a sense of the size, of the volume, the cubic yards of stuff that would be accumulated over a period of time? 250 specimens per event, per patient seems like a lot to me.

DR. CHAPMAN: It is. I'm not sure when my agency agreed to do this that they quite understood how many specimens this could be, although I tried to tell them. But let me start with your last question first, how many cubic yards of space do we have. CASPIR is developed, actually it's, all the storage is in vapor phase liquid nitrogen and by my calculation the number I've heard tossed around in terms of number of Xenotransplantation procedures that have been done under FDA IND has been around 200. By my calculation, if there have been 200 and each of them has 250 specimens the day we announced the availability of this archive various sponsors decide to send to us, that that would probably immediately fill two of the large liquid nitrogen vapor phase containers. How large a proportion is that of the available space? Not very significant. I've gone into that with people. I can't tell you off the top of my head.

What I can tell you, and what's already been discussed in my preliminary discussions, is that this is fine for the volume of procedures occurring now, but if the volume increases significantly, what we will probably be told is that we have to go to some other contractor-operated mechanism or find a way to purchase additional space because this collection will not be allowed to usurp a large enough proportion of the storage space that CDC as a whole is back where we were ten years ago, where we were discarding valuable specimens. So if we suddenly had some great clinical successes in xenotransplantation, this may be a temporary solution and we might have to find another one.

The question before that, I think, was what was the longest time span that stored specimens had actually been useful in answering questions, and the Pontiac fever is one that you gave that was a good example. And the Hanta virus pulmonary syndrome outbreak in 1993, Rick Goodman said, gee, this sounds just like that death I investigated as an EIS officer, and I'm not sure how long Rick had been at CDC, but I think it was over 20 years, and he was actually able to go back and confirm that that death had been due to Hanta virus pulmonary syndrome and that was published, and I believe we must have had stored specimens for that and I think that would have been about 20 years.

Probably the biggest application has been with early AIDS epidemiology where there were either collections of

serum from Africans collected for various applications, viral hemorrhagic fever is, I know, some of the stuff that had been collected in the early days of Lassa fever investigations in West Africa, which would have been in the probably mid-1970s were some of the collections that were then useful in the initial determination of AIDS, population-based AIDS prevalence in that part of West Africa after the virus was available, which would have been the mid-'80s, so that would be about 10 years. There were also collections of sera for various hepatitis projects that were 10 to 20 years old that were used -- that had been stored appropriately and were used for this purpose.

And we have in our -- in a smaller investigation, I've been involved in some studies where we've been looking at people occupationally exposed to nonhuman primates who have become infected with simian foamy virus, which is a nonhuman primate retrovirus that appears to be benign, but in going back and trying to identify duration of infection with archive serum, we have in some instances been able to get archive serum that was more than 20 years in the past that was sera positive.

Some of that serum was archived by the Army and we have some people who had been in the Army in certain projects and we went back, lo and behold, it was still available. There was at least one, we actually had someone at CDC, most of them the published reports will say documented duration of two to five years. That basically is how far back we were able to get an archive specimen, but some of them, we had specimens at least 20 years back, either stored at CDC or stored elsewhere.

DR. SCHECKLER: So it's about 20 years and some of it is serendipity and some of it is planned.

DR. CHAPMAN: In the last investigation I told you about it was largely planned, and many people who employ, people occupationally exposed to nonhuman primates routinely bank sera annually or two to five years, including CDC, to investigate exposures. When hepatitis collections were useful for HIV, that were a loss of fever collections for HIV, that was clearly serendipity.

DR. ALLAN: I have a question, Louisa. Let's say that this database is in place and you've got the biological specimens and five years from now, ten years from now there's some sort of a new virus in pigs or whatever, and the CDC investigators get all excited and they want to go screen all these biological specimens to see if there's -- first of all, if the pigs have the virus and whether or not the patients have been exposed or have the virus. Is there anything in place to -- and this is in a scenario where there's no adverse reactions and there's nothing to suggest any disease association, which is more of basically a research interest on the part of the investigators. Would they be able to screen the samples or do they have to get approval from the sponsor or?

DR. CHAPMAN: Well, they would have to get approval but not from the sponsor. Part of the issue with public health ownership of these specimens is that it's going to have to be set up in such a way that sponsors release proprietary rights. We can't store this collection and then be in a position where sponsors can say I'm afraid of that question, I don't want the public health authorities asking it on my specimens, or I don't like the outcome, you can't publish it. So not from the sponsors.

But would they have to get permission? Yes. Who would they have to get permission from? The person who can sign administratively for release of these specimens is the designated administrative custodian, which will be the office of the director, DASTLR.

But there are also -- I didn't go into all the details, but the way CASPIR is set up, there are scientific custodians as well, and basically what -- there will have to be a considered decision about whether the questions proposed to be asked have significant enough value to the public health that it's worth risking not having the specimens taken for that investigation, not having them available later for other questions anticipated that may come up.

Who will make that decision? Well, it will obviously be the public health authorities. It's not going to be one investigator and it's not going to be the administrative custodian alone. It will probably -- what will probably happen in effect, I don't know what will be written in the protocol but what will probably happen in effect is that the two agencies that are going to be accountable to the public for safety with these investigations, which will be FDA for product safety and CDC for outbreak investigation, emergency response, preventive medicine, will have to agree that the release of these specimens for this purpose is justified and worth no longer having them if

something else comes up later. So it's not going to be anyone's scientific curiosity or their desire to promote the field.

They might be released for the kind of thing you are describing if there's going to be real benefit to knowing is this a new introduction into pigs, is it just a new recognition of something that's been there all along. Can we find it in the pigs that have been used in the past for people who 20 years after exposure are still healthy and so on? But not just because somebody thinks, gee, this would be great and I can make my name here.

DR. VANDERPOOL: Louisa, this is a naive question following John's far more sophisticated one. When you talk about specimens how many times can they be tapped into before they are gone?

DR. CHAPMAN: Well, before, every time that you take a specimen through a freeze-thaw cycle you risk losing some viability. So when it talks about archiving, like when the guidelines said ideally you should minimally archive no fewer than 10.5 cc plasma. .5 cc's of plasma is actually a pretty small volume. And the tubes that are manufactured intended to store plasma in vapor phase liquid nitrogen standardly come in 1 or 2 cc volumes. So the reason for recommending it be in such small volumes is so that you can thaw one without having to thaw the others and then parcel out from that one.

DR. VANDERPOOL: So how many do you have per specimen take? We have several of these vials of 2 cc specimens?

DR. CHAPMAN: What's outlined in the guideline -- right now we don't have any of these specimens at CDC. But looking at what's outlined in the guidelines and assuming that will more or less reflect what the individual INDs that have gone forward under FDA review have put as their standard collection because they may have proposed something slightly different and justified it for their trial, when you add up the specimens that are recommended to be collected from the source animal at the time the tissue for the xenotransplant product is acquired and at necropsy -- well, the ones recommended at the time the xenotransplant product is required the biopsy of the product. The ones recommended to be collected from the human recipient twice before the transplant, immediately after, at one month, six months, one year, two years, and then every five years and then estimating how many five-year intervals there may be for life and estimating a certain number for autopsy from the human and from the animal, came up with about 250 individual specimens which would be multiple ones from each time point for each procedure, not each trial, but each procedure within a trial.

DR. KASLOW: Question about ownership: Implicit in your description of the proposal, it seems to me, is that you have planned to forbid the institution or the manufacturer from retaining duplicate specimens?

DR. CHAPMAN: No, no.

DR. KASLOW: You are not? Cap.

DR. CHAPMAN: The intent behind this is to have an archive of specimens that can't be used for anything else and therefore will be available if they are needed for a public health investigation. The sponsors are free to collect anything above and beyond what they want for their own purposes of investigation or their own storage or whatever.

DR. KASLOW: But it seems to me, then, that some of the controls on the uses of these that you are outlining here are sort of moot if they are duplicate specimens available for somebody else to do whatever they want.

DR. CHAPMAN: Yeah, well, our concern with those controls would not be in forbidding certain investigations, just forbidding that these specimens be used up for these investigations.

DR. KASLOW: But the information that would come from them could be potentially the same, so in effect you are permitting duplicate use and the potential for information to be produced that you might otherwise choose not to have produced or disseminated.

DR. CHAPMAN: That's okay, I mean, you know.

DR. KASLOW: Well, I think you might want to think about that.

DR. CHAPMAN: Well, I don't think that we, I don't think that the government wants to be in the business of limiting, other than through the human research subjects oversight as appropriate for ethical reasons, of limiting the investigations here. What we don't want to do is be in a position where there's a public, what appears to be potentially a public health emergency and we don't have the resources to investigate it.

DR. KASLOW: I understand, and I'm not suggesting that you should or shouldn't forbid, but it seems to me that the implication of allowing duplicate specimens to exist and to be used for purposes that may be contrary to what the government intends to do with them even during an emergency outbreak situation ought to be considered.

DR. CHAPMAN: I'm not sure I'm understanding you, but what's coming to mind is you are thinking that people might ask questions, publish the results, raise issues that then require us to deplete these archives to address concerns raised by those issues.

DR. KASLOW: No, I'm concerned that there may be more than one approach to an investigation of a particular problem and a company or an institution or an investigator might choose to use those specimens, take a different approach and come up with a different answer that would be potentially conflicting. That happens all the time in science, of course, but I think that you are making such a strict control of these specimens and placing so many guidelines on their collection and storage, that the implications for what happens with duplicate specimens that might be taken I think should be considered a little bit more thoroughly.

DR. CHAPMAN: I'd like to -- I don't want to take up the time here but maybe I may contact you as I work on this proposal to get a better sense of what your thoughts are.

DR. KASLOW: Okay.

DR. GROESCH: We need to move along, but if there's just one or two very quick questions, let's go ahead.

DR. SCHECKLER: I want to disagree with Dr. Kaslow, my colleague. The only reason for having this is the decision that we needed to keep these specimens for 50 years, and the public comment, including the comment of our own committee, that said that's not feasible from a point of view of sponsors staying in business, et cetera, et cetera, et cetera, so the only reason for this is a public health insurance policy with a concern about some unexpected or long-term viruses such as prions or such like. And that's the reason for having it at the CDC where they could do the laboratory part of the epidemiologic investigation.

How important that is, how big a priority that is, I can't say, but I don't have any problem at all with sponsors doing what they currently do in keeping specimens for as long as they want for their own reason. That's a different entirely type of issue and problem.

DR. KASLOW: I don't have any problem with it either, but it seems to me that our lack of a problem with it should be explicitly included as opposed to implying by all these complicated legal discussions of ownership that might get tangled up later on in who can use those duplicates or what they say about the investigations or studies that are done.

DR. GROESCH: I'd like to thank both Louisa and Eda and Jim Foss and Tom Kruthers for the presentations we've had this morning, they have been very interesting and helpful. We really appreciate it.

Agenda Item: Ethics for Committee Members

DR. GROESCH: And the next session is on, a very brief session on ethics training for the committee members. I would like to start out with a statement that you've heard before and you will probably hear again in the future, but it's just a very brief statement about the rules of conduct in conflict of interest.

Reminder that as members of this committee, you're special government employees and are therefore subject to rules of conduct that apply to government employees and these rules are encompassed in the standards of ethical conduct for employees of the Executive branch. And each of you received a copy of this document when you were appointed to the committee.

At every meeting in addition to reminding you about the importance of following the ethics rules, we always like to review the steps that we take and ask you to take to ensure that any conflicts of interest between your public responsibilities and your private interests and activities are identified and addressed.

As you know, before every meeting you provide us with information about your personal, professional, and financial interests. And we use this information as a basis for assessing whether you have any real potential or apparent conflicts of interest that could compromise your ability to be objective in giving advice during committee meetings.

If such conflicts are identified, we either issue a waiver or recuse you from a particular portion of the meeting. We usually waive conflicts of interest for general matters because we believe that your ability to be objective will not be affected by your interest in such matters. And we also rely a great degree on you to be attentive during our meetings to the possibility that an issue should arise that could affect or even appear to affect your interest in a specific way, and in those cases we would ask you to recuse yourself from the discussion.

The next part of this is a new session for you and that's dealing with confidentiality. And we are very fortunate to have with us today Mr. Holli Beckerman Jaffe. She's the ethics counsel within the Office of the General Counsel in the Department of Health and Human Services.

MS. JAFFE: Good morning. Just to reiterate what Mary had said, I've been doing this for over ten years, and really it's not worth your trouble to even go near something if you think there's even an appearance because you are all going to spend a lot more time explaining why it's not a problem than it's really worth. So I'm available, I would be very happy to talk to you to advise you in any way I can. But if you even think it's an appearance, it doesn't have to be an actual conflict. A lot of times it's not an actual conflict, it's just an appearance and somebody runs with it, and then you spend the next three years of your life explaining why you really did nothing wrong. That's really a waste of your valuable time. So I just want to say, please, give me a call.

What I really wanted to focus on today is you are going to be seeing some confidential information. And what you need to just remember is that you are getting this information in your capacity as a government employee. There's a criminal statute along with a regulation that says you have to keep this confidential. So I don't think that this would be any surprise to you, but we just want to really explain it in a little detail and give you an opportunity to ask any questions.

So as Mary said, you are special government employees, which you all realize you are bound by the government statutes and regulations and that you need to be sure that anything that's kept that's given to you during the closed sessions you keep to yourself, just amongst the other committee members, and that you don't share that, particularly that you don't take this back to your other jobs and do something differently at your other jobs based on the confidential information; that you are using this information only in your capacity as a special government employee, as a committee member.

This is really what I wanted you to focus on. Any time you see Title 18, that's criminal statute, so hopefully that will get your attention. This is not up to me whether or not it's prosecuted. This really goes to the IG, the Inspector General, at the Department of Health and Human Services and then on to the Assistant U.S. Attorney, whether or not they want to prosecute it. And to be honest, they tend to go for the big fish. So as a special government employee, you are considered to be a high-level employee and so you really want to be particularly careful.

And it's just like I said before, whatever information you are given here, you are told that it's confidential, you need to keep confidential. And particularly trade secrets. You know, you don't want to take that back and do something to use that, misuse that in any way. A violation of Section 1905 could be up to $1000, not more than a year in jail or both, including removed from the committee.

And then even if it would not rise to the level of disclosure of confidential information is that you violate 18 U.S.C. Section 1905, it could be a violation of the standard of conduct. And I believe you all have been made familiar with those. And specifically it's Section 2635.703, which is misuse of nonpublic information. So an employee shall not engage in financial transaction using nonpublic information. That's kind of like insider trading stuff, that you might see something that impresses you with the company or doesn't impress you with a company so you may think differently about a competitor. You don't use that information to your advantage or somebody else's advantage and you don't disclose any of the information that you hear outside this room.

You want to keep in mind that as special government employees you only work as a special government employee maybe a few days a year, but these rules apply to you 24-7, 24 hours a day, 7 days a week, and if you are given confidential information we refer to it as lifetime ban, you always need to keep that confidential. So even once your appointment ends as a special government employee, you're given confidential information, you always need to keep it confidential until it becomes very clear that it's nonpublic information. And you may want to check on that, make sure that -- I mean, it's probably obvious to you, but again, it's criminal statutes which always make me nervous, so I like to be double sure on that stuff.

And this, like I said, when it becomes nonpublic is pretty much, I'm sure you would understand when that would become, but to get nice and legalistic on you because that's what they pay me for, here is a nice definition of nonpublic information. If it's routinely exempt in the disclosure of the Freedom of Information Act, that's generally trade secrets. A lot of times private businesses either are required or voluntarily submit trade secrets to the government with the understanding that it can't be released, so it would be exempt under the Freedom of Information Act. I don't know if you are familiar with that, but it's basically a statute that allows people to write to the government and request particular information.

They could write to the government and try to get a trade secret and the government will say no, that's exempt from disclosure, we can't disclose it. So just like the government generally, the agency, HHS or FDA, could not disclose it, you as special government employee also could not disclose it. It is designated as confidential, which this information clearly is, or has not been disseminated to the public.

Now, really the difference between the statute and the regulation is the regulations say you can't disclose confidential information or you can't make it appear that you disclosed confidential information. So doing something even slightly different could raise questions. So you want, like I say, keep these information just to yourselves, keep it here in the committee and don't take that outside of the room. Again, sorry, not to beat you over the head with this, but there are some really serious violations for disclosing the confidential information, particularly that you need to go home and separate your striped clothes from everything else, you could wind up in jail, not too much fun. And then also discipline or corrective matters which could be as special government employees, clearly you would be removed from the committee and you would not be getting an appointment any time in the near future after that.

We are going to ask you to -- Mary, are you going to be handling -- okay. We are going to be asking you to basically acknowledge that you understand what we are talking about here, that you should not disclose this information. We ask you to sign this confidentiality agreement and you'll get a chance to read it again. It points out the criminal statute as well as the regulation and it's saying that you will not disclose the information and you will keep it confidential.

And really to protect everybody we've set up a couple of steps here to make sure that the information does stay in the room. So that we are asking you again to acknowledge it and you are going to sign the form. Sorry I got my transparencies out of order, I just realized.

Wherever possible confidential information will only be verbally transmitted to you, it will not be given to you in writing. And that's really to help you. It's very easy, we get a ton of paper. It's very easy to get papers mixed up, and we want to try to help you and make this as easy as possible and when possible just give you confidential information only verbally. But if you are given materials, we will most likely collect it back from you.

If we do need to send you information over the next few months or years, we will be sending it in a tracking system, either through FedEx or certified mail. If we have to fax it to you which we tend not to do because it can, I've been told it gets into the fax machine, it could be there for, I don't know, years. So we'll try to not fax stuff, but if we do have to fax stuff to you, we'll let you know it's coming so that either you or a designated person can be there to get it right from the machine just to make sure that it doesn't, that nothing happens to it. And lastly, as I said, just discuss this information amongst yourselves, with other committee members, and not with anybody else.

Is there anything on what I've just said or anything just generally on ethics that I could --

DR. VANDERPOOL: Thanks for your report. Any questions from the committee are certainly welcome at this point.

I want to say that one of the challenges to understanding what's going on in clinical trials has been the negotiations between Mary Groesch and others regarding what will be presented to us in closed session. Maybe the limitation are these requirements via confidentiality and the possible criminal penalties that go with that. The great advantage that we have for such closed sessions is that without them we really can't get the information we need to be able to make considered judgments about the ethical regulatory and other issues. So the very positive side is this puts us inside information that is very sensitive and precisely because we are wanting to do that, then these confidentiality requirements are necessary.

MS. JAFFE: Exactly. And that is one of the reasons. There's another statute that allows the government to disclose this to designated people such as yourselves, and because there is such a great benefit from it. Exactly. Let me also give you my phone number. I said you could call me, but you wouldn't know how to do that. (301) 402-2576. And I'm officed at NIH.

DR. GROESCH: And I can also give you that information. And I just also want to point out that everything that Holli went through you have received in hard copy today, and then tomorrow I will be passing out -- you have the form, too, to sign, but I also have a special pink version of it that you can sign tomorrow that we'll collect. And we will also be asking even any federal employees who will be in a closed session tomorrow to look over these materials and to sign this form as well.

DR. ALLAN: I just had a question for Eda. You put out a draft about the possibility of changing the status of clinical trials, at least in xeno and gene therapy. Is there any update on that?

DR. BLOOM: We have received a great deal of commentary on that, as you might imagine. And we are in the process of trying to revise -- that was a proposed rule, and trying to revise that proposed rule according to the commentary. It's actually a very daunting task because as you well may imagine, some of the commentary was quite comprehensive, but it hasn't gone away if that's what you are asking.

DR. GROESCH: Eda, do you think that it might work out if our next meeting is in March, that we could hear about that or depending on what the status is?

DR. BLOOM: I think it would depend on what the status is. As soon as there is a possibility to discuss it absolutely.

DR. VANDERPOOL: Okay. Ms. Jaffe has made herself available for any questions that any of us would have. So let's take a ten-minute break and let's be back here, maybe it's a little more than that, and start right at ten till 11:00 because we want to give the next exciting set of meetings due time in our schedule.

(Recess taken -- 10:39 a.m. to 10:55 a.m.)

DR. VANDERPOOL: Let's begin to gather together. All of those outside, begin to take your seats.Let's begin our session on meeting updates, news and advances. And our format for this will be that Mary Groesch will introduce the respective speakers. And then after the speaker finishes, we will have some time for discussion. Mary and I have sort of set out a time line here. And if the discussion is fervent and rather lengthy, we'll have to

break the discussion regarding the topic that speaker has initiated and presented and then hope to be able at the end of the session to revisit whatever questions we have about any presentations from any of the speakers before our lunch break Mary, introduce the first speaker, please..

Agenda Item: Xenotransplantation: Meeting Updates, News, and Advances.

DR. GROESCH: Thank you. Our first presentation is on highlights of the Sixth Congress of the International Xenotransplantation Association, and we are very pleased to have with us Dr. David Cooper. He's an associate professor of surgery at Harvard Medical School and is affiliated with the Transplantation Biology Research Center at Mass General Hospital and he's also the editor in chief of the journal "Xenotransplantation." Thank you.

DR. COOPER: Thank you. I'm going to review very briefly some of the highlights of this meeting that was held in September, October in Chicago, the Sixth Congress of the International Xenotransplantation Association. We have a meeting every two years. And I'm going to be very selective about what I'm going to talk about. There are several people in this room who were there and they must forgive me if I don't mention what they presented, but I'm going to pick out really some things that I think would be of most interest to you. And this is based not only on my own considerations, but as editor of this journal I got half a dozen people to give me their highlights for publication. So some of the comments I'm going to make come from what these other colleagues of mine have put forward.

And I think we can generally say that clinical xenotransplantation will take longer to come through, particularly from an organ transplant perspective than we originally hoped some years ago. And this has been dawning on us for the last few years, as I'm sure it's dawned on you, but we still think it's a little way down the line, not sort of tomorrow.

But the good news, there appeared to be no new major obstacles that we have not already thought of presented at this Congress. Now, you could say the xenotransplantation will be introduced clinically within a relatively short time, but that would be if you were geologically speaking. So that gives us quite a bit of leeway here, but I think that's quite a good comment.

And you'll remember that the dean of Harvard Medical School in the 1920s said that half of what the students had been taught was wrong but unfortunately he didn't know which half. And probably half of what I'm going to tell you today is wrong, but I don't know which half.

Now, the first thing is that we are making a little progress. You can remember that if you put a pig organ into a baboon or a monkey, you've got a pretty good chance it's going to be rejected within a few minutes or hours if you don't give any treatment, and certainly a good chance within 24 hours. But you can see that now we've got life supporting kidney transplants, pig kidney transplants in baboons that have been recorded up to 75 days, in monkeys up to 90 days. So we are making a bit of progress. And I think actually Nextran have just got one over a hundred days.

But if you look at the mean or the median survival, it's around about a month or five weeks in the best groups. So we are still struggling, but we are doing better than a few minutes, the one exception, and Robin Pierson will back me up on this because this is his particular field of interest, is the lung transplants. The lungs appear to have all sorts of problems. We're not really, I think, completely sure whether they are immunological or physiological or whatever they are, and most lungs will not survive more than 24 hours no matter what you do to them. So the lung is a special problem.

Now, as you probably remember from when I had the privilege of speaking here a couple of sessions ago, the big problem is this antibody. We have antibody in ourselves which is directed against the target on the vascular endothelium of pigs, which is a galactose sugar, so we call it anti-Gal antibody. You can think of it to some extent as a pig's blood group. It isn't a pig's blood group, but it's rather similar to when we transplant across the A, B, O barrier in humans.

And I got to come back to these Gal conjugates, which was one of the main themes of this meeting, that people

are producing these Gal conjugates to try to absorb this antibody. But before I go on to that, also not from the Congress but recently there has been announced from Dr. Xu in New York, that he probably has identified another antibody which we have that is directed against pig tissues that we naturally have, and it's an anti-Neu GC. (phonetic) It's another sugar on the surface of the pig organ and that will be difficult to test because baboons do not have these antibodies against this glycolyl neuraminic acid. The only animals that do have this antibody is humans, so it's going to be very difficult to test this in an experimental model because there's no animal model that differs from the pig in this respect.

There were virtually no new drugs that were announced that have any effect really that we believe on xenotransplantation survival. So there was nothing much in the pharmacologic area. And one thing that wasn't in the pig-to-baboon or pig-to-monkey model but it gives you an example here, in the rat-to-mouse heart transplant model where antibody plays a role, if you take specific pathogen-free mice, very clean mice, the rat heart will live on average about -- sorry, if you take nonspecific pathogen, very dirty mice, the rat heart will survive on average about six days. But if you take very clean mice housed in special conditions, et cetera, SPF mice, the same heart will survive a mean of 33 days. So the antibody can be upregulated or maybe new antibodies come in by the environment that we live in. Now, obviously the humans that we are going to be dealing with are going to live in a normal environment so there's nothing much we can control about those. But there are a lot of factors that obviously modify the antibody activity.

Now, coming back to these Gal conjugates, you remember that the vascular endothelium of the human has three sugars on it basically, where we have the A, B, O blood group sugars, not only in our red cells, it's on our vascular endothelium, every blood vessel that's in the body has this on it, either A or B or whatever your blood group is. And the same point here, the pig has this galactose sugar. This is the key big difference between the two species.

And we used to have this galactose sugar like other animals, all other mammals had this galactose sugar, but somewhere along the line the Old World monkeys, apes and humans, this gene that makes this sugar was deleted several million years ago, 20 or so million years ago, and so the pigs will have the sugar, we don't have the sugar. And as a result we make antibodies against this sugar. And that's why we have these antibodies.

And if the antibody binds to the sugar on the surface of the pig organ, it will cause complement activation and other changes which will cause rejection of that pig organ. So it's initiated by this antibody binding to these linear sugars. And the idea of these Gal conjugates that several groups have now manufactured, these are backbone structures of different sorts that have multiple Gal molecules, multiple sugar molecules on them, and when you put them in -- you put them in intravenously into the animal, into the baboon, for example, the sugar binds to this conjugate which is in the blood and therefore it is -- sorry -- the antibody binds to the conjugate in the blood and therefore the antibody is no longer free to bind to the sugar on the surface of the pig organ. So these are Gal conjugates that are mimics of the sugar on the pig cells. And by mopping up this antibody, probably also taking it to the liver or other places where it's metabolized, these Gal conjugates continually deplete the blood of this antibody.

Now, it's not a hundred percent, because I'm sure this antibody has a choice of going onto this Gal conjugate or going onto the sugar on the surface. And disappointingly the survival time of pig organs put into baboons that are being continuously supplied with one of these Gal conjugates is not significantly longer than when you don't give the Gal conjugate.

There's less rejection, there's some other features suggesting that you are doing something good, but it hasn't really extended survival significantly. But this is one approach to this problem. But the ultimate result is a little bit disappointing.

Here is one example from our own lab, this is the antibody, the IGM and IGG levels. You put in this conjugate here, marked in black, put in a large amount initially and then a sort of steady intravenous infusion, and as soon as you put in the large amount, the antibody drops to nothing, you can't measure it again until you stop the conjugate, and then it slowly comes back.

One thing that we've noticed and the Nextran group have noticed particularly is that when it comes back, it

comes back very slowly. It doesn't just jump back to the original level. It may take quite a while to get back to its original level, and therefore it does look as if we are doing something here to perhaps suppress production of its antibody by tollerizing perhaps some of the B cells or plasma cells that make the antibody.

So the return of antibody is slow, but eventually it comes back to the original level. So surprisingly, even in virtual absence of antibody, it hasn't prolonged survival as we would have hopped. So the opposite approach, and there was a little bit of work on this at the time meeting, is to go to the pig and see if we can't have a pig that does not express this sugar. If we had a pig that didn't express this sugar, obviously there will be no target for these very specific antibodies, so that would be one problem hopefully out of the way.

We have pigs that have human complement regulatory proteins on them that have some protection against this rejection, but the aim is to try to get what we call Gal knockout or GT knockout, standing for the enzyme galactosyltransferase, where this gene that makes this enzyme, that makes the sugar has been knocked out of the pig.

Now, until recently this knockout technique, although it was possible in mice, was not possible in pigs for various reasons, but with the nuclear transfer technology, it is now theoretically possible to do this. You can take an adult cell or an embryonic or a fetal cell from the pig, you can knock out the gene in vitro in the lab and then you can clone a new pig from this modified cell. So that you ultimately should have then a pig that is normal in every respect except that it doesn't have this particular capability of making this one sugar.

And Tony d'Apici from Australia, who is very interested in this field and is doing a lot of work in it, he predicted that obviously you need to knock out both of the pair of genes. He predicted that somebody would announce this year that they had a pig that did have a knockout, was a knockout pig, that means it had lost one of these pair of genes, and that by breeding from them or further knockout, we would have a totally Gal-free pig within the next couple of years that we would then test in the pig-to-primate model.

So he was optimistic. And I think there were two or three speakers there on this topic, they were all optimistic that they are in the pipeline. And I think if this were the case, this would be a significant, a major breakthrough for the field of xenotransplantation because the one big hurdle we appear to have at the moment is this Gal antigen, anti-Gal antibody problem, and if we have no target for this, I think it would give the field a great leap forward and we would be able to see what is the next problem down the line.

One extra point here, though, is that one of the groups from Australia pointed out that he's now discovered a second gene that makes the same sugar. Now, if that is correct, you'd have to knock out both of the genes, so it's going to get a little more complicated, but the essence of it would be the same.

And I mentioned that this can only be done through this nuclear technology, which you remember Dolly was the first sheep, and it's a fairly complex system, mechanism. You read last week that they've got somewhere in cloning humans in this way. And you take the nucleus of one pig and you put it in the cell of another pig where you've removed the nucleus and then you end up breeding a pig from this original, which has the characteristics of this original cell that you took the nucleus from.

And pigs have been cloned. Several groups have now cloned pigs using this technology, cloned normal pigs using this technology, and the question is can they actually come up with a Gal knockout pig, and obviously that pig we think would be perfect for our situation.

Now, I say that it's going to happen and Tony d'Apici says it's going to happen, but bear in mind that any absolute assurance is a good definition of psychosis. So we're still in a little bit of doubt.

Now, there were several other topics that are of interest to us. One, this is from our own lab, if you put a pig organ into a baboon, you get a steady drop, at least we do in our lab, a steady drop of fibrinogen, which suggests the fibrin is being deposited, the fibrinogen is being used up and eventually you end up with a state where you can actually bleed, the baboon can bleed because he's used up all his coagulation factors. This is just one example.

And we've had quite a bit of trouble. Other groups have had less problem. There was a little bit of work on this presented. And we are still not sure is this entirely an immunologic phenomenon, that if we had no antibody problem it would not occur, or are there some physiologic differences between the pig and the baboon that will actually make it occur anyway.

There was a little bit of work on tolerance induction, probably the most likely area that is going to come to success is something that Megan Sykes really originated, and that is thymic transplantation. You take the pig's thymus, transplant it into the baboon. If you can get the thymus to engraft, the thymus reeducates all the cells in the baboon and says don't reject anything from the pig any more, it's reeducated. Then you put in a pig organ and it's not rejected. This doesn't get over the antibody problem but it should get over all the subsequent problems. So this is encouraging.

There was very little on the physiology between the pig and the baboon. Very little new came out of the differences in physiology between the two. I promised Jay I was not going to say anything about infection. But I will just mention that at the meeting there were several papers on xenoses. The PERV problem, which you know about, there was a lot of data from the use of bioartificial livers in humans, using pig cells in the artificial liver, from groups that have tried to infect various animals, including nonhuman primates, with porcine endogenous retroviruses. There was the patient study from the immerged pigs that seemed to be incapable of infecting human cells or baboon cells with this endogenous retrovirus. Although they have the virus, they don't infect primate cells.

And there were various studies about various breeding practices. And generally speaking, from all of the groups that presented data, it seems that the PERV problem is becoming much less of a problem than we once feared. It seems very difficult to actually infect primate cells with PERV retroviruses. So that was good news. And there was work on other viruses, cytomegalovirus. Again, two or three groups showed that if you take the piglet away from the sow at a very early stage, within a few days, they do not get cytomegalovirus infection, which they would get from the other pigs or sow, and therefore they are free of this virus. And we think this would be the case for several other viruses as well. So the overall message from the meeting was that the infection problems are not going to be as much of a concern as we thought perhaps two or three years ago.

Finally, there was a little bit of information from the group, you may remember, they put baboon bone marrow cells into a human about five years ago. This is the human, and I know Jonathan Allan was on the committee that gave permission for this to be done, and I know he didn't really think it should be done, I think he abstained, but this patient who did not really benefit significantly from the bone marrow cells, he was a patient with AIDS, didn't benefit, but he has no sign of any xenosis, he has no sign of any infection. This was presented at the meeting.

This is something that I think will be very important for you. There was one paper of some islets that have been prepared, pancreatic islets for treatment of diabetic patients. They've been prepared in New Zealand. I am reliably told that the New Zealand government would not give permission to this small company to do this trial in New Zealand. So they shipped the islets to Mexico where they were put in about 11 children. And they said some of the children benefited, did not seem to need so much insulin and so on; although, the data was a little bit inconclusive.

And many of us were concerned about this example of xeno tourism, where you can actually take some pig islets in one country, ship them to a country with very limited regulatory framework and do the trial in children. And, therefore, this is something that we have to really consider how are we going to regulate these trials that are being done to get around regulatory authorities in one country and go to another country. So this was of considerable concern to us.

The other thing that I think will be interesting. Martine Rusblatt (phonetic) who is a lawyer in the Washington area, I believe, she has calculated that the number of xenotransplants worldwide will eventually be about a hundred thousand a year and she says the worldwide cost of monitoring those from the point of view of infection, et cetera, et cetera, will be something in the region of 10 billion dollars. And she suggests that we have a tax on every xenotransplant, every patient that gets a xenotransplant, somebody pays $10,000 into this fund in order to monitor worldwide what's going on. And that's an interesting point.

Now, this is where we are at the minute, to sum up. We are doing pretty well with the transplant field. We would like to get into xenotransplantation. This seems to be the answer to us. And so we set up and we start putting pig organs into baboons and they all get rejected very quickly, so we use some of these conjugates and we do a little bit better and then we find there's a PERV problem and we try to sort that out too. And finally we actually get a knockout pig and the PERV problem is solved and we think we really have reached the big time and that we have now solved the problem. But there is always the possibility of another problem around the corner.

And this is where we are at the minute. We think the problem is going to be solved, but, in fact, I suspect there is going to be problems around the corner. And to quote the inimitable Dan Quayle, the future will be better tomorrow. And I think that may be the case but we may be in this situation: There are two Golden Ages, the mythical one in the past and the mythical one in the future. We may be fooling ourselves that the one in the future is going to be better than the one we have at present. Thank you very much.

DR. VANDERPOOL: Questions or commentary for Dr. Cooper, who has given us his usual classic presentation, enthusiastically and laced with all good humor. Does Dr. Sykes or others have comments to add or questions and so on?

DR. SYKES: Yes, I do. David, just a comment on the second Gal transferase discovered by the Australian group. I believe they thus far have found that this transferase is used mainly to glycosylate intracellular glycolipids and haven't found evidence that it leads to cell surface expression of Gal. So I think that's an important thing to bear in mind at this point. We don't yet need to be too concerned until we've learned more.

Second thing I would like to just add that we heard a bit about, at the Congress, was the use of fish islets as potential islet transplants for humans. There's a species called Tilapia that there were several papers describing the ability to actually genetically modify them so that they can make a human insulin and there's possible potential there that perhaps we might want to hear about more in the future.

DR. KASLOW: Is there evidence that the anti-Gal antibody has a natural protective effect against other human pathogens? Is there any reason why we would not want to deplete that antibody?

DR. COOPER: Yes, there's good reasons. We think that we get this antibody, we are not born with it, we think we get it when our gut is colonized with bacteria viruses. And there are a number of bacteria viruses that actually have Gal on the surface and we think we developed antibodies as a protective mechanism. And we have found in our experience, that the pig-to-baboon model, that if we block those antibodies with one of these conjugates for quite a long time, that there's a slightly higher incidence of getting infections in the baboon with these gastric bacteria. So there could be a very good reason why if we could knock it out of a pig and retain that protective mechanism it would be very good.

DR. LUBINIECKI: Is there evidence from other species that a homologous GT knockout is viable?

DR. COOPER: Well, we don't have a GT. We knocked it out naturally at some stage and we are fairly viable, I think. And certainly the mouse has been knocked out and that's completely viable. Uri Galili, one of the experts on this antibody, is suspicious that the pig won't survive because he says that there's a huge amount of it in the pigs, up to 500 times as much as in the mouse. He thinks it must be doing something physiologically. But there are others of us who are more optimistic about it. As we and the mice can survive without it, then probably the pig will be as well.

DR. SYKES: Just an issue that we've heard a lot about in the xenotransplantation field, and I didn't hear any real follow-up on it and I wonder if maybe you did, is this question of accommodation, which is for those who are not familiar with it, it's a situation whereby normally a graft would be hyperacutely rejected by the presence of antibodies against its endothelial cells, but there are some situations that have been described, for example, with some A, B, O mismatch transplants where antibodies can recover but not cause any damage to the graft, despite the fact that the endothelial cells do express the antigen.

And there's been a lot of work to try to understand this phenomenon, and there have been claims that it has occurred in the pig-to-primate model but not really very good data.

I'm wondering, David, a few years ago there were some data from, I think Columbia University where neonatal baboons lacking natural antibody were transplanted with porcine organs and this was shown to avoid hyperacute rejection. It seems to me that would be an ideal situation for accommodation to occur because then the antibodies come up slowly after birth in the animal and the graft is already placed. Have you seen anything to that effect?

DR. COOPER: They haven't done anything more and they, in fact, they didn't treat those baboons so they all developed cellular rejection rather rapidly, within a few days, so they didn't get hyperacute rejection because the absence of the antibody, but they got other problems. And that was a very difficult model to organize because they were using very young baboons, they were very small.

What is disappointing is that although as you say it occurs in some humans with an A, B, O mismatch, they have anti-A antibody and they have an A organ there but they do not reject it and we still don't really understand why. It's been shown in several rodent models, it's been shown in vitro in cellular models where you can get cells surviving despite the fact that you put antibody on that should normally kill them through complement activation.

Despite all that, nobody has really conclusively shown in the pig-to-primate organ transplant model, even when you have antibody coming back very slowly as I showed you with that conjugate, nobody has really ever conclusively shown that you can get accommodation in that model, which has been very disappointing to us. So I'm not totally optimistic about it.

DR. MENDEZ: She asked my question, because in our series of A, B, O incompatible patients, a great many of them did have gradual rises in their antibody levels, anti-galactose levels to very high levels and yet did not reject. As long as it happens slowly and over a prolonged period of time, they would develop very high levels and they would be just fine.

So in the 78 days, in the 64 days on the pig-to-baboon there must be some other mechanism. Do you postulate that's cellular rejection?

DR. COOPER: We believe that even these longer-term surviving baboons, it is primarily an antibody media to defect, that there is some cellular rejection, but it still seems primarily it's related to antibody, either the anti-Gal antibody coming back again or possibly to new antibodies that are developing after exposure to the pig organ.

In our laboratory we believe that we've been able to block the induced antibody response and the rejection is all related to the natural anti-Gal antibody which slowly comes back, which means it's more of a problem than we thought. So we think it's still primarily antibody, and if we could get over the antibody problem, I would be personally, and I think others in the room would be personally very optimistic that we could actually get a significantly longer survival because we think we can deal with the cellular response much better.

DR. VANDERPOOL: Let's have one more question, then we'll need to move on.

DR. CHAPMAN: Can I make one comment that's not actually part of this discussion since the questions seem to be over but probably should be on the record. During the break I had an opportunity to talk with Dr. Kaslow and some other people in more concrete terms that helped me understand his concerns, and just for the benefit of the people in the room and for the record, I am now aware of the importance and wisdom of developing a written material transfer agreement for any specimens that are released from the biologic archive for investigation, whether government investigators or private sector investigators, that would address both what they were allowed to use those specimens for and limitations on their ability to retain them or share them.

DR. VANDERPOOL: Thanks. Let's move on to the next presenter.

DR. GROESCH: Thank you so much, Dr. Cooper.

Our next presentation is on recent data about infection in xenotransplantation. Our speaker is Dr. Jay Fishman. He's an associate professor of medicine at Harvard Medical School and also in the infectious disease division at Mass General Hospital. Thank you, Dr. Fishman.

DR. FISHMAN: Thank you all very much for inviting me. What I'm going to try to do today is to cover a variety of topics in the area -- and I hope they are related topics -- in the area of infection in xenotransplantation. I'm not going to give you a true overview of xenogeneic infection. You've heard a great deal about it. What I'm going to do is give you a personal perspective on xenogeneic infection.

I'm going to present a couple of topics related to cytomegalovirus and porcine endogenous retrovirus that are new or nearly new in terms of data and try to make these coalesce in some form or another into a cohesive package or more or less cohesive package in terms of where I think this ought to take us.

The questions, I think you know, are fairly straightforward: Does the risk of transmission of infection due to xenotransplantation outweigh the potential benefits of xenotransplantation? Are the concerns about various infections realistic or not? When will we know if infection occurs? Will it occur in 5 years, 20 years? And I have to point out that this is in the context of dealing with transplantations every day who have infections throughout the course of their lives after getting allotransplants.

And how do we monitor, perhaps the most important question, how do we monitor for these infections and which agents do we monitor for? Years ago I broke down the potential pathogens into four categories, three of which have some assays available. Certainly the traditional zoonoses toxoplasma that we see in transplantations, primarily derived from cats, are agents known to cause infection in immunosuppressed humans in particular, but in humans in general.

There are species-specific microbes and this is always subject to reinterpretation, but organisms that tend, for the most part, to be restricted to their native host species, so that you may be able to get, for example, cytomegalovirus to go across species lines, but in general it tends to stay in its own species, and there are some assays available for those pathogens.

Organisms of broad host range. We are all familiar with adenovirus -- am I not turned on, you want to turn it on. Thank you. Organism of broad host range -- I think it was better before. Okay. Organisms that you are fairly familiar with, adenovirus, reovirus, that although they tend to occur in humans, they may occur in many species and tend to not be restricted to one or another species and for those, there are many assays available. In theory, those three categories are organisms that we could breed out of any donor species, in other words that would be amenable to testing and removal from a breeding colony.

The problem is with the unknown organisms, and the first example of this was porcine endogenous retrovirus, but in fact we are talking about a whole spectrum of potential pathogens, theoretical pathogens, or nucleic acid recombinants, novel pathogens created either in the donor or in the host or, in fact, new manifestations of old diseases, organisms that have been identified in swine cause disease in humans that are, in fact, quite different from those that have been seen in their native host species. In general, the risk of infection is thought to be greater in xenotransplantation for some of the reasons you heard David Cooper refer to in that we are manipulating the recipient and the donor more than we need to in allotransplantation. We bypass host defenses by the direct implantation of organisms into the recipient. That organ itself provides an ecologic niche; i.e. culture plate, from which these organisms can grow.

Because of the direct cellular immune system you will have a protected or relatively protected immunologic site from cellular immune function. Obviously we may not have the assays to detect these, as I've mentioned, and we may not recognize clinical infection when it occurs, and all these will contribute to enhancing the risk of infection. So that the goal of meetings that we had starting back in the mid-'90s was to identify the lists of organisms that were potential pathogens that were of concern in the potential xenotransplant recipient.

It turns out that even many years, or at least a number of years later there were relatively few data on which organisms will provide a specific microbiologic risk to xenotransplant recipients. And the problem is if we have

to immunosuppress these recipients, as seems likely, that all organisms are potential pathogens. We have worked with the hypothesis that the organisms will be similar to those that we encounter every day with allotransplant recipients, kidney, hearts, lungs. But the reality is this is a hypothesis that may be incorrect. The biologic behavior of specific organisms, say derived from pigs, cannot be predicted.

My own hypothesis is the potential risk to the community is, in fact, from unknown organisms whose pathologic behavior is not known and can be transmitted in the absence of clinical symptoms. HIV might be an example. The initial infection is very modest. Subsequent disease may not develop for many years after exposure.

This is what I call my surgical slide. I say we do it and trichinosis be damned. My apologies, David. For those of you who think that the risks have been overemphasized, have been exaggerated, you may very well indeed be correct. The question is how do we approach this.

The initial concern was greater with viral infections. The reason is they are transmitted easily and carried by many tissues. The reason we're concerned about viral infections in the allotransplant arena are threefold. Certainly cytomegalovirus provides the best example. Each of these viruses directly causes infectious syndromes: Retinitis, nephritis, hepatitis, inflammation, injury to organs, directly to the organism.

Each of these organisms has immunologic effects as well. So the viruses all tend to be globally immune suppressive. So if you have cytomegalovirus, you are more likely to get other infections as well. They also have pleiotropic cellular effects in that they tend to upregulate or change a variety of cell surface molecules that increase the risk of graft rejection so that they are globally suppressive but, in fact, enhance the risk of graft rejection, which is an adverse outcome, and most of these viruses have an effect on the derivation of cancer. Most of these viruses to one degree or another stimulate inflammation and contribute to oncogenesis.

We know from past experience that bacteria present in both allotransplantation and xenotransplantation are present which are the main stimuli for activation of latent viruses. Amongst those are the immune responses themselves which are stimulatory for viral replication, immune suppression, which amplifies the virus, once activated. Cytotoxic agents in radiation therapy, commonly used agents. And infection, inflammation, cytokines, every time somebody has a fever, every time somebody has a graft rejection episode, every time they get the flu, you are more likely to activate viruses and, therefore, this event is fairly common.

I'm just going to take you through two of these. The first is cytomegalovirus. Cytomegalovirus was selected initially because this is the single most important infection in the solid organ transplant world. We see it in the vast majority to one or another degree of our patients. This particular section from the lung is of a baboon xenotransplant recipient of a porcine kidney. And as you might see, there is a dark area in the center of this cell. That is the classic OI inclusion of cytomegalovirus, viral infection in a xenotransplant recipient.

We decided that it was very important to develop quantitative assays for this infection. And I should point out that the first effort in this regard was Marian Michaels, who tried to develop molecular assays to baboon-derived cytomegalovirus a number of years ago in relation to the baboon marrow transplant experience. What we have done is taken advantage of the quantitative polymerase chain reaction system, which is just illustrated here, and I like this one because it's very colorful, but basically what we are able to do is using molecular markers, quantitate the amount of virus in any individual. And we've developed assays for baboon cytomegalovirus and for pig-derived cytomegalovirus. And the question is very simple. If you take a standard regimen for xenotransplantation, put a pig organ into a baboon, nonhuman primate recipient, what happens to the endogenous viruses, what happens to cytomegalovirus.

The first thing that we saw is that the baboon, the host, the recipient cytomegalovirus was increased dramatically in virtually every tissue, therefore we know that any virus that is latent in these individuals will be reactivated. Perhaps more troublesome from a xeno perspective is the fact that the porcine virus was also upregulated in the graft and that porcine cytomegalovirus is also found in all the baboon; i.e. recipient, tissues. Whether or not it's causing active infection or just the spread of free virus throughout the system we don't know. But the reality is we know that both donor and recipient virus is activated in this combination.

The obvious answer was to try to abort this kind of infection by using the drugs that we use standardly in xeno --

in allotransplantation. Ganciclovir, for example, is a commonly used antiviral agent. In fact, the use of prophylactic ganciclovir does not seem to impact the replication of porcine cytomegalovirus. So we've got a virus that is potentially spreading throughout the system for which we currently do not know of effective antiviral agents. So it is important to think in the context of common viruses, not just PERV, may be important in the xenotransplantation arena.

The second area that I would like to touch on is the porcine endogenous retrovirus. And you've heard from experts much more articulate than I talking about porcine endogenous retrovirus. But the point I would like to make is the importance of the assays that you use and the control assays that you use in these kinds of studies. There is a tendency to sample in xenotransplantation studies peripheral blood, it's accessible. And what you then say is I have a negative assay and therefore this individual is not infected by PERV. That may be true, but it's not necessarily true. The problem is if you have infection in your brain or in your big toe, will the blood necessarily reflect that infection? And the answer is we don't know. We need to do the proper controls. We need to be sure that we are doing the assays properly because we know that these assays, as wonderful as they are, are complicated. They are difficult assays to perform. And what we want to know is not is there porcine endogenous retrovirus DNA around. We know that's going to be present wherever there are pig cells. We want to know is there PERV RNA, is the virus replicating, has it gotten into the host, what is the risk to recipients and are we measuring the right material.

And therefore, we have gone ahead and done, very much as for the CMV, is develop a variety of assays for pig-specific markers, for baboon-specific markers, and for PERV which are reverse-transcribed assays, RTPCR, which look at the RNA, look at viral replication as opposed to the presence or absence of virus. And so this is the approach that we have taken to thinking about it. And we get -- we now have some standardized assays that we use for PCR, quantitative assays for porcine endogenous retrovirus, that can be used not just on blood but on serum and on multiple tissues from the body to ask the question, is PERV spreading during the course of xenotransplantation? Is it occurring early? Is it occurring at all? Is it occurring late? We don't know, but these are the kinds of tools we need to use and the kinds of tools we need to insist on from clinical trials to address the question for any pathogen of whether or not infection is occurring. Because when infection occurs due to retrovirus or any new pathogen, we may not know it, or we may not know it for a very long time. And there are a lot of reasons why we won't see retroviral infection clinically for many years even though it may be occurring.

I would remind you of some data that you've seen from Clive Patience in the past related to PERV which I think are probably the most current and important data, which are that it is possible to select animals that are relatively free of transmission of infectious PERV, a virus that is infectious for humans. That's not to say it's an absolute. I don't think in this case I would claim that, but basically that much like CMV we can breed animals for whom the risk for infections seem to be markedly reduced if not eliminated so that this is a major advance in this setting and is largely derived also from his study which shows that the infectious PERV is actually a recombinant strain of virus which is not A or B or C but in fact a combination between those various strains and, therefore, we can predict which virus is likely to be infectious and which virus is going to be likely noninfectious. And these are important advances.

What I would like to do is spend my last couple of minutes talking about infectious disease surveillance, which is not my bailiwick. But what I would like to do is broaden the discussion a little, which is to say that what we need in surveillance may be what we are getting and more. The problems are the following: If we are looking for infectious events as a result of xenotransplantation, there are some agreements that need to be had. There has to be some consensus regarding the list of pathogens we are talking about. But there is no such consensus. We need data on the risk of infection, talk about informed consent, but in fact we don't really have many relevant data outside of PERV and now CMV on potential pathogens in the xenotransplant environment. And we need assays that are reproducible that everyone in this room could perform in the same way on the same tissues and those don't exist.

The other problem is that we are looking for known pathogens, that we are looking for clinical syndromes. You saw the database, we are looking for fever, chills, all of which is very reasonable. What if there aren't any symptoms? What if we are spreading infection in a way that is not clinically relevant? Then it's too late by the time we are making the diagnosis. Looking for specific pathogens we know of is a little bit like the drunk looking under the lamppost because that's where the light is. The idea is, in very simple terms, we need to look

beyond the pathogens that we know about. We need to look for new pathogens because the unique risk of infection in xenotransplantation may relate to organisms that are unknown, have silent transmission, are asymptomatic, established latency and all those things that we have talked about for the unknown pathogens.

If we use standard surveillance paradigms, can we discover what may be novel nonclinical syndromes? And I would suggest that we need to focus instead of looking for the organism of the week, which endeavor I helped start, so this is not pointing fingers, if we can begin to focus on looking for unknown pathogens, unculturable pathogens, look not just at archiving but routine testing, questions that came up before, how long does a sample last? Rather than just collecting samples and storing them against events, insist that what we are looking for are new pathogens, that we need to test each patient for new samples, each patient's new samples for the potential of new pathogens.

And what this will require are some rather sophisticated but universally available molecular techniques, differential display, microarray, which will then allow us to begin to look for pathogens that we don't know anything about. And this is in conflict with standard surveillance. And these are quotes from a variety of documents which basically illustrate that we are looking for specific problems. Case detection will be done by health care workers based on standard definitions. Surveillance is disease or syndrome specific, adverse events.

What we need to do is generate the science of xeno infections at the same time we are doing the immunology. I would point you to three important reports, all of which I think you probably are familiar with. There was the idea that xenotransplantation should generate enhanced surveillance. Exact definition, arguable. But some very nice meetings that were put together by Marianne Laderoute and Andre La Prairie for Health Canada suggested that we needed to enhance surveillance in response to xenotransplantation. And those documents are available on the web.

Louisa has already pointed to the U.S. PHS guidelines that evolved over a very long period of time. But Louisa herself was one of the main movers for specimen archiving, the importance of storing away specimens against future scientific endeavors.

I would focus, though, on a conference which report came out about a month or so ago, which was the OECD WHO consultation on xenotransplantation surveillance which was held in Paris and organized by a lot of efforts of Elettra Ronchi and Clara Witt which had as a goal establishing practical framework for international xenotransplantation surveillance, and amongst the discussions that came out of that was the concept that Eda has already presented this morning, which is the idea of controlled vocabulary, the importance of reporting systems that are universally available.

I give you one example and I think that this field has changed in light of what happened on September 11th. I took one day's newspaper, happened to be the New York Times, but picked a variety of articles that sparked my interest. The issue of derivation of embryonic stem cells on murine feeder cells with the risk of contamination as a result of exposure to murine cells. A series of international deaths that occurred due to chemical contamination of dialysis membranes across five or six countries. The use of hamsters for detection of anthrax. Potential bioterrorism due to small pox and an article on xenotransplantation. And what all of these have in common are a series of unexpected or untoward detrimental health effects. And so I think the challenge should not necessarily be to develop surveillance which is xenotransplantation specific. Yes, we need that. No question. But in addition, we need something which is more international in scope and which will capture xenotransplantation issue, which is an international health reporting system which uses standard definition, standard reporting tools and computer software and interfaces, free exchange of information which will capture unexpected events in the health care world.

And I would refer you to the late Jonathan Mann's grandmas network, because when he wanted to track AIDS in Africa, he went to the oldest woman of each tribe and said, what's going on in your neighborhood and got a wonderful representation. And we do this in medicine often. We call each other and say, have you seen one of these. The reality is we need an Internet-based grandmas network to capture not just xeno but infectious disease, unusual deaths, adverse events, and to take a new approach to this whole issue, which is not context dependent as was, for example, the detection of anthrax in Florida.

So I'm done tilting at windmills, I thank you. And thank you very much for having me.

DR. VANDERPOOL: Okay. Do we have questions? I think we are going to have to limit them to five minutes of questions and answers and hope to be able to revisit this at the end of the session.

DR. ALLAN: The study that you were involved in with the porcine CMV in baboons, I guess the question I have is you looked at essentially the DNA found in the cells within the baboon. Did you look for cell-free plasma or did you actually look for activation?

DR. FISHMAN: We didn't look at RNAs, we looked at CMV, DNA in multiple tissues, both in plasma and in cells, in leukocytes and in multiple organs, and they were fairly consistent. There is a high level viremia that's occurring. I don't know yet whether it's intact virus or not.

There also is chimerism. There are intact pig cells that are migrating to multiple tissues throughout the baboon's body. There is a discordance between the pig cell genomic markers and the amount of virus. That doesn't work as it does for PERV. It's not a marker of infection, chimerism, because CMV is an episomal element. So the reality is there is a suggestion that certainly chimerism is occurring, that free viral spread is occurring. I can't yet say whether or not infection is occurring. I can't exclude the fact that infection is occurring, so it's still possible.

DR. ALLAN: Barbara Potts was here and showed that porcine CMV does grow in human cells and tissue culture, so.

DR. FISHMAN: Yeah, and actually doesn't grow very well, you can force it but it doesn't grow very well in baboon cells. So there probably is a defect with the model in terms of the parallel with human. My guess is that it doesn't grow well and my experience is it doesn't grow well in human either, but the fact is you can make it grow. Is chimerism going to make it grow, in other words would that force the system? It could happen.

DR. ALLAN: And the follow-up question, what is your feeling about -- I mean, you've focused on viruses. What is your feeling about fungal infections, bacterial infections, parasitic infections? All are a concern, but all those should be able to be dealt with at the breeding level. I mean, we deal with fungal, parasitic, bacterial infections routinely in allotransplantation. If these hosts are immune suppressed, those infections will occur. But they shouldn't be donor derived.

In other words, in the allotransplant setting it's very rare to see donor-derived infection. In fact, it's reportable for most cases in the literature. So we do see it occasionally, we will see pseudomonas, we'll see other bacterial infections. But, in fact, most of the infections we see are environmental. Those should be able to be bred out of any donor colony. But if you had, let's say, a fungal in pigs that doesn't cause any disease in pigs --

DR. FISHMAN: No, but we can identify those. Yeah, we should be able to identify them. The question is reasonable, I mean, how carefully can we breed the pigs and that's the limit, but we should be able to test for those. In other words, we have assays that currently would work for those, put it that way.

DR. SYKES: Jay, what you showed about the porcine CMV viremia in baboons is very important and compels me to remind everyone that David Cooper told us earlier about a study showing that CMV can be bred out of pigs by early weaning, so I think your data really shows the importance of making sure that we use CMV-negative pigs, which is possible.

DR. FISHMAN: Yeah, and the only caveat to that is there may be other organisms that we need to exclude also, but, yes.

DR. SALOMON: I think everyone would agree that particularly with bioterrorism as a very real threat, not that it wasn't a real threat a year ago, but now we're all aware of it again. It would be great if one could design strategies using these new technologies of high-through-put screening and genomics, et cetera, to find new organisms. That's easy to say. Do you have any ideas about how you would do that?

DR. FISHMAN: Yeah, I do. We have available a variety of libraries and microarrays and other resources that I think we can use for that purpose. The problem is what you need, for each species you need another set of microarrays and reagents. It's costly in terms of initial setup, but if, for example, you are doing pig-to-human xenotransplant, it is the kind of cost that could be spread very easily amongst a large group of investigators. For example, pig microarrays could be used by people doing atherogenesis research because it's used in a variety of cardiac models, bypass models, could be used by pig breeders, could be used by xenotransplant people. In other words, the net cost could be spread across a greater range of individuals. What we have are some resources that we are going to try to use to illustrate that purpose. We don't have those data, but we are going to try to go forward with that. Yes, but it's time consuming, it's costly. As it would be for any new surveillance tool.

DR. VANDERPOOL: Jay, to what degree do your thoughts on surveillance at this point call us to revisit the public health service guidelines on surveillance and maybe re-think some of those guidelines? Is too much being done in some areas that is wasteful and things not done in other areas that you view as essential? Or are we that far along at this point to revisit those guidelines?

DR. FISHMAN: I think the guidelines might be seen as a minimum that's required. I think what's in the guidelines is very important. Clearly what you've heard already today, the archiving of specimens, the development of a database is critical, are critical and need to go forward. I think we all agreed on that in the earlier discussions. The question is can we take an approach perhaps based on the model of xenotransplantation that has broader health implications, both for xenotransplantation and others, and I would suggest in going back to what Dan asked, which is can we develop resources which would be useful for screening populations for disease for adverse events, chemical injuries and others that would have broader health implications than just xenotransplantation.

I'm concerned that the many things that I've been proposing for years in terms of xenotransplantation are too costly, are not practical, but put in a broader context of health prevention and put in the context of the recent events may be more practical than what we thought about. There may be an opportunity to bring public health into the molecular PCR and other eras, which is being done at a lot of centers but not on a cohesive basis.

DR. KASLOW: I will just make one brief comment and Marian or Louisa or others who may know more than I do about other systems: There is at least one crude system that I'm aware of called Geosentinal in which the tropical medicine folks have banded together in effect to provide sort of interchange over the Internet, a web-based system for surveillance of particular diseases that they've chosen as sort of models because it's a small unresourced system. But I think there are beginnings of the kinds of surveillance systems for that approach that you suggest.

DR. FISHMAN: Louisa and Eda were at the meeting I was at in Paris and they are more knowledgeable in this area than I. I think there are as you say models in the European union and others, most of which have specific dedicated resources, but in fact are what you say, could be linked potentially.

DR. VANDERPOOL: Let's move on to other speakers. Thanks so very much, Dr. Fishman. The next three reports should be considerably briefer, so we are still hoping for some time at the end.

DR. GROESCH: Our next speaker is Dr. Judith Massicot-Fisher from the division of heart and vascular diseases and the National Heart, Lung and Blood Institute, which is part of the NIH. And Dr. Massicot-Fisher will be talking about a workshop that she had organized over last summer on xenotransplantation.

DR. MASSICOT-FISHER: I thank you for the opportunity to come here and tell you about our working group meeting last summer. A number of people in this room attended. Megan came and Mary came, Shiv came, Louisa was there. People from the FDA were there, so I think we had good representation.

I would like to tell you a little bit about the institute before I go on. The mission of the National Heart, Lung and Blood Institute is to provide leadership for a national program in diseases of the heart, blood vessels, lung and blood. The NHLBI is the second largest institute at the NIH and in fiscal year 2000 its budget was 2 billion dollars. And I use fiscal year 2000 because I don't have transplant dollars for 2001.

Transplantation, the institute sponsors basic and clinical research in transplantation of the heart, lung and bone marrow. In fiscal year 2000 we spent 66 and two-thirds million dollars on this transplantation. Out of that 66 million, 27 million was spent for solid organ transplantation. Now, what you need to also keep in perspective is that transplantation competes with a lot of other therapies for end-organ failure, such as the total artificial heart, left ventricular assist devices, cell transplantation, and that's also competing with things like high blood pressure research, atherosclerosis research, so a small piece of the pie, in essence.

However, I think we really appreciate the need for more organs because, as you can see here from these statistics, in 2000 there were only about 2200 hearts transplanted from humans and less than a thousand lungs. Currently on the waiting list there's over 4,000 people for heart transplants and almost 4,000 for lung. However, these figures are really deceptive because they are just the tip of the iceberg. Because there's such a low probability of getting a transplant, a lot of people just never make it to the waiting list and there have been estimates of 20 to 40 thousand people who could actually benefit from a heart transplant if hearts were unlimited. And that's why we would find xenotransplantation so exciting if it was to be successful because it would totally open up transplantation to a lot of people that now have no opportunity.

One of the things that we spent some time talking about at our working group meeting last summer was how the institute approached a project like the artificial heart program. Now, this program goes back many years to the mid-'60s. It was actually mandated by Congress and Congress actually gave the institute money to start the program. With this, the institute provided leadership, a critical mass of investigators, annual meetings so that these people could come together and have a synergy. And there were over the years a series of contracts that were let out for various components that were needed for the artificial heart, like one year they might put out a contract to look at valves. Another year they might put out a contract to look at energy sources. And so it wasn't until the mid-'80s where they finally brought all of these contracts and components together for a mechanical heart.

Now, industry did manage to keep all their proprietary rights to these and the institute did not claim any -- what should I say -- any benefit from it in essence. Industry was then free to go on and commercialize it and make it marketable. Things like we're seeing today like down in Louisville to the total implantable heart.

So this program also encouraged people by coming to these annual meetings to share with each other, and I think that was one of the things that came out in our meeting last summer, that maybe in the xeno field some company that had sort of already gone down certain paths whereas with the artificial heart the institute was right there from the beginning sort of keeping things moving along. Working groups are actually sort of internal advisory meetings or groups advising the institute on scientific needs.

In this case interest was expressed by the community that the institute should have this meeting. It was held in Bethesda July 30th. The co-chairs were Verdi DiSesa and Jeffrey Platt. And we tried to include every group that we thought would be interested or playing a role in xenotransplantation. We had people from academia, we had people from industry, we had people from all the federal agencies that we felt had a role. And part of the reason for inviting the other federal agencies was that if a question came up that wasn't within the purview or the mission of the institute, we would have someone to say that NHLBI can't solve this, but someone here from the FDA can tell you what is being done, or someone from CDC like Louisa could tell you what's being done. So we wanted to get all of the hurdles out there and we wanted to have all of the players in the same room at the same time.

So we have a long list of hurdles. And I tried to group them for you. First, probably maybe foremost, are the scientific hurdles, some of which we have heard about from Dr. Cooper's presentation. They are the immunological barriers. There's what's called acute vascular rejection. There's also the antibody problems, and antibodies do play a role in acute vascular rejection. One of the things that I think had more discussion than I had heard previously was perhaps a problem with some of the animal models that these pigs have human complement regulatory genes in them and you put then this pig heart in a primate and these complement regulatory genes are not going to work to the best advantage. So the fact that you are only getting 30 or 60 days survival of a heart or a kidney may be somewhat of a problem with the model itself rather than the whole approach to xenotransplantation.

There's the physiological barriers such as the intravascular coagulation that we see that maybe some incompatibility of coagulation control. Certainly the infectious diseases problems where we heard about from Jay and others in other meetings.

I think what's sort of maybe is sort of not addressed in some ways because it's sort of a behind-closed-doors kind of thing is the high cost of performing these studies. I mean, it costs a tremendous amount of money to maintain clinical grade animals. The cost of the nonhuman primate model is very expensive. I'm told it can cost $30,000 to just do one heart transplant. When you think of that and you think of how many need to be done, it's kind of staggering.

Reagents for large animal models, when you want to bring in new monoclonal antibodies and new reagents, the idea and the cost of preparing these in the quantities needed for a large animal model are very exorbitant, and there's also the cost associated with the long-term primate and patient follow-up. Certainly keeping these archives going is not a cheap project.

Other hurdles, then, are sharing among academic investigators and industry. Company A has a pig here with these genes in it, Company B has a pig with other genes in it. Well, gee, maybe the best pig would have both genes but how do you get these companies to come together protecting their investment in their pigs and their ideas, and it's kind of a -- it's not something you can sort of put the people in the room and force them to collaborate, but hopefully sometimes when you do bring people into these working group meetings, collaborations do come about just by people talking on the coffee break, well, maybe we should be working together or maybe we can work out these legal hurdles to us collaborating.

There's the protection of the intellectual property rights. There's the liability issues. Other hurdles that we perhaps talked about less because they were somewhat one step removed maybe from the mission of the institute, but certainly new investigators need to be attracted to the field. It seems when you come to any of these meetings, it's the same faces that you are seeing that maybe a few fresh faces, a few new ideas could help get over some of these hurdles that we've been grappling with over the years.

Public education so that every time you see xenotransplantation in the paper it's not in a negative context. If you could get it out there so that people could appreciate, yes, there's risks but, yes, if it were to work, the benefits would be absolutely staggering.

If you thought about, when somebody is saying a hundred thousand people could benefit from a xenotransplant, I don't think that is really that far afield if you threw in kidney, heart, liver, all those people, with such few human organs available, just now have no opportunity.

The next steps now are we need to take the summary of this meeting, the recommendations, finalize a report, present this report to the institute where those recommendations are going to compete with other working groups' recommendations, other priorities within the institute and we have what's called a board of external advisers that looks at all the initiatives that come along and they meet twice a year in April and September. And then once that group has sort of ranked the initiatives, we also present initiatives to our National Heart, Lung and Blood advisory committee that meets four times a year.

Always with these working groups and workshops we publish a report. Dr. Vanderpool, I can tell you that he participated in a working group last December on tolerance and that manuscript is published, it came out in the journal "Transplantation" last month, so we do get these things out so that the community knows the meeting was held, sort of gives us an idea of what the flavor of the discussions were and what the recommendations might be and then just sort of follow along to see what the institute can afford to do. I will be happy to answer any questions.

DR. VANDERPOOL: Thanks so much, Judith. One thing I see in this is I need to collaborate with you, continue to collaborate with you. I know part of the purpose of this is for funding and we have in the very next presentation some ideas about better funding. So let's stay in collaboration and see what we need to do with you and perhaps now for the first time you are doing something for us by letting us know what you are doing. Thanks so much.

DR. GROESCH: Our next presentation is by Dr. Robin Pierson. He is an associate professor of surgery and cardiac and thoracic surgery at Vanderbilt University Medical Center. And Dr. Pierson is presenting a xenotransplantation consortium concept that I believe may have arisen out of this workshop that we just heard about.

DR. PIERSON: Thank you very much, Mary, and thank you very much for the opportunity to address this group. What I have to say today is very much a work in progress and very much a dream. Jay Fishman referred to Don Quixote tilting at windmills and I think if anybody's to be accused of that, I certainly fit that description. I am a heart and lung transplant surgeon with scientific and I hope some day clinical interest in xenotransplantation.

And let's see if I can get back to the first slide. And I want to talk to you about some discussions I've been having both with industry, with the NIH, and with the academic community about ways we can address the significant problems and obstacles that we perceive standing in the way of clinical application of organ xenografts.

You just heard from Judy that there's a tremendous well-defined, well-understood large deficiency in availability of organ and cell grafts which could be addressed by xenografts should we become wise enough to know how to do them. Thus far you can argue about the number on the front of all those zeros, but there has been a tremendous financial investment by a number of different companies and academic institutions and governments in this field. The result is, has been in addition to many other advances, that production and development of transgenic pigs expressing complement regulatory proteins. And while these pigs represent a step forward, neither those pigs nor all of the other allied technologies have gotten past the problem of delayed xenograft projection, which David Cooper outlined for you previously. So until we understand that problem, its solution is unclear. And in that context, from the perspective of a commercial entity, I would argue that there is, in fact, at the moment no marketable product in sight.

Novartis has for that reason stepped back considerably from their interest and enthusiasm in developing this as a clinical product. I don't know that Baxter has been quite, and Nextran, have been quite so public about their plans in this regard, but I think it's the perception of all of us in the field that industry's enthusiasm for going ahead with this is greatly reduced as a consequence of what we learned about the obstacles in the last several years.

Judy has also, I think, covered and Jay and David have already covered the various specific obstacles which I've attempted to summarize here. I would only say that the scale of the financial commitment necessary to address these residual problems is similar to what's already been plowed in. And if Big Pharma is not going to do it, who is?

The final point on that slide was that the intellectual property associated with the developments made so far is tied up in the companies who have made those investments, and if we are to get past, get to the next level, in my perception and I think that xenotransplant community agrees, we need to find ways to bring that intellectual property under an umbrella and get it working together. And as Judy mentioned, if we can start developing pigs that have not one transgenic modification but multiple, then we are in a position, I think, to begin to make progress in understanding and dealing with the scientific and technical barriers to success.

From a technical perspective, the things that we need to do are not straightforward. Introducing multiple different modifications into the same pig is difficult. And once you have done that, selecting out the pigs, propagating them on a scale, which is useful doing large numbers of xenotransplants in primates, is not trivial, again it's hard. Validating efficacy, we need to standardize our models, we need to have reagents which actually work well in nonhuman primates to address the specific scientific questions we need to answer. Using reagents designed for mice or for humans may not answer those questions and investment is required to provide those reagents so that we really can begin to understand the problem better.

Finally, something that Jay brought to my attention is that people are working on sequencing the pig genome. That project would have relevance not just for the area of xenotransplantation where it might help us to deal

with physiologic problems as they increasingly become clear, but also in atherosclerosis research and in other scientific efforts and of course agricultural efforts which depend on the pig.

So in summary here the problem is big. It's an international problem. It is an international scale problem which is going to require a lot of money and a lot of focused expertise to solve. So I think this is to some extent redundant but I just wanted to summarize that there are a number of different pigs on the ground, or at least alleged to be on the ground in this case, of the Gal knockout which are defined in various ways which might be useful for transplantation.

In my estimation it is going to require an "itteradupe" -- and I apologize for the typo -- but it's somewhere between interactive and iterative process is going to be necessary for us to make progress on developing the pig which will eventually be useful. And I would also like to point out, as others have previously, that for different organs different needs may be identified, and if we are to develop different pigs for each of the different organs, that is going to be, again, an order of magnitude bigger project than any given company is going to want to take on at the beginning in each case for a smaller market.

So the scale of this and the size of this and the scope of this problem is not one that is readily amenable to a single company or even a small group of companies taking on. And I submit that the way to approach this problem as a society, both as a xenotransplantation society, which is one place that this idea has been aired in our meeting with the NHLBI and more broadly now in this context, this discussion that we are undertaking is how to address this on a structural level.

The proposal that has emerged from the dialogue initiated at Judy's meeting and carried on subsequently around the coffee table at the IXA meeting last October was the idea to merge the intellectual property that exists in the currently, current transgenic pigs and inbred pig populations, to merge that technology into a consortium structure.

Now, the details of what that is going to look like are a very important question, residual question. And, in fact, those kinds of details are perhaps critical to whether this will actually come into existence or not. But from my perspective what needs to happen is for the intellectual property to be entered into a single entity which will establish some value, probably in the form of shares in the existing pigs and which will both allow and, in fact, reward subsequent intellectual property to be invested in the process, just as a joint venture between companies would go on today. And if the company, if it is as attractive to the companies which have IP and specifically the two, I think, dominant players here are Baxter and Novartis, if they are willing to cooperate and work together, I think many of the other companies which have very interesting ideas and technologies which are going to be, in fact, critical to this effort, I believe that will catalyze the chain reaction of cooperative interactions between industry which are focused around this effort to produce xenogeneic organs for transplant.

That will in turn help the scientists who also need to work together and to not do things in duplicative fashion, to do things in a way which allows us to learn in mechanistic ways about each of the specific issues that we face in this field and in addition to allow organ-specific approaches to be developed. Reagent access in addition to the cataloging functions which the FDA has identified and already made substantial progress on, the FDA could really help us by helping us interact with the pharmacology industry, the Big Pharmas, they have many reagents that we would love to use in our animal models; however, if those drugs or reagents are being tested in preclinical circumstances, the data from our work in nonhuman primates is subject to review by the FDA, and if we kill a baboon in the context of giving it a particular monoclonal antibody from Company A, Company A's preclinical trials could be put on hold. Not that that would necessarily happen, but the risk of that is not one that pharmacologic companies are willing to take, and therefore they simply won't let us use reagents in that context, at least not freely. So that barrier is one which from a regulatory perspective would be wonderful to have go away, or at least to be addressed in a way which allows us to function. And again, this is a context in which dealing with a consortium as opposed to ad hoc, one by one with individual companies would really, I think, facilitate progress in the field.

Finally, the financial aspects of how to go about funding something that costs -- is likely to cost half a billion dollars and take ten years, I would submit needs to be regarded like the moonshot or like developing alternative energy power tran supplies for systems for alternative fuel vehicles. Those are projects on which international

cooperation has been applied and has, in fact, succeeded, at least in part, in generating things which are of value to society. I think that progress is going to be incremental and it's going to require an iterative process, but I think it is possible if those reagents can become available.

Let me skip this and go directly, in interest of time, to what I've been working on in trying to stimulate discussions between Baxter and Novartis. And I would say that those discussions are at a very preliminary stage. They have in fact occurred at least once before and not led to fruition for reasons which are not entirely clear to me, but fundamentally the two companies did not see the value of working together. It's clear from those discussions that if we can put together a framework which is perceived to be of potential benefit to both of those corporate entities and, in particular, if it provides access to capital, to funding which will subsidize, if you will, the development of pigs and to protect them from liability as well as to deal with reagent issues, that is the kind of carrot that may induce the cooperative interaction that many of us believe is necessary to build better pigs.

How are we going to decide what experiments get done and in what order and what the strategy will be for addressing the specific problems. That consortium governante structure needs to be sorted out in a way which is suitable, which is attractive to both the corporate world, to the NIH, and to academia. And I think the catalytic question at the moment is whether we can persuade the NIH to provide substantial support, either in the form of complicated series of multiple program project grants focused around core facilities generating and propagating transgenic pigs or in a less formal relationship, perhaps similar to the one that's been devised for the tolerance network whereby a certain amount of money has been set aside by a combination of institutes and private entities to support work on an important problem which, again, has a large scale and requires a long view of the problem and its solution.

So of the many various things that we could do to the pig, if I could have a pig that had all of these properties, I would be delighted, but getting there is going to take a lot of hard work. And it's going to depend on access not only to these various substrate pigs, but also on the development, as David Cooper alluded to, nuclear transfer technology or stem cell technology for the pig, both of which exists to some degree, but the various bits that are crucial to actually getting pigs produced in large scale, that has not yet been demonstrated with genetically modified animals.

So in addition to the consortium or arising out of the idea of forming a consortium, I've been in conversation particularly through Judy Massicot-Fisher with various program representatives at various institutes of the NIH and have been advised that the way for us as a community to go forward in our scientific exploration and as in the looking for a way to support the consortium financially with U.S. government resources would be to form something like this thing that I've named CAPAX. The root word would be capacious, which also translates in Latin into fitful or capable and also great. So I'm hoping that it will be all of those things to all people, of course, Don Quixote, obvious and all of that.

But the mission of this umbrella organization would be to provide the governante structure and the scientific direction for a group of activities focused on generating pig organs for transplant. And how this is organized is something that is, I hope, I hope there will be reason for the discussion to go on and for people to work on building a structure which they are comfortable with and which will be effective. So the components that would be considered by CAPAX or figuring out working with the consortium, of course the consortium being essentially the business entity, the academic effort would presumably fall under their purview and would include participation both by corporate funding mechanisms as well as by government funding mechanisms and I would submit that the NIH even on an international scale would offer a mechanism for oversight and credibility that would perhaps be quite valuable if they are willing to serve in that capacity. It certainly is not in their current brief. So and these are, listed below are some of the other objectives that I think are reasonable. If I may have a few minutes. If I can stop here or I can talk a little bit about what the current state of play is around the world in other countries. What would you --

DR. GROESCH: Well, I would like to hear it but we are running a bit behind. You will be around today, right, and maybe it could come up maybe in a context of discussions later. Would that be fine?

DR. PIERSON: That would be fine.

DR. GROESCH: Is there just like maybe one question that we could take now if anyone has for Robin?

DR. SALOMON: Could I just make a comment. I think this is a very bold thing that I support theoretically. Two things, these should not be brief, but I'll make them brief. The first is that I think what really should come from the NIH, in my opinion, is a guidance to create some cores that just are not generally going to be well-supported in industry. And I think one of the big problems in this whole xeno field has been that the science fell short, and when things stopped working it was really difficult to stop and go back and say, why were these animals dying at 30 days, 40 days and 60 days. And I think David pointed out to us that's still unknown. We need to focus there.

The other area would be in infectious disease where clearly companies found that to be a very daunting task and there could be cores created for that. And lastly, cores for genomics, I think that's an extremely powerful technology for both basic biology and screening and infectious disease.

The last comment that I make also briefly is this should be international. And you clearly understand that, Robin. But the work going on internationally is every bit as active right now as that going on in the United States and I really wouldn't like to see this consortium concept isolated to one or two companies in the U.S.

DR. PIERSON: The goal is naturally to be inclusive. The challenge is to get there. And the route I see toward that is to ask the dominant people whether they are willing to cooperate. If, as I mentioned, if they agree, I think that could catalyze a subsequent series of interactions which would be attractive to NIH and other funding agencies on an international scale.

DR. GROESCH: Thank you. I'm sorry to cut the discussion short, but Robin will be around. And I believe he will be attending the working group session as well. So we are going to move on to our final presentation for this session and that's by our chair, Dr. Harold Vanderpool, who will be providing us with some highlights of a recent position statement on xenotransplantation.

DR. VANDERPOOL: In the tradition of the academic study, I will seek to convey the tone and substance of this important 2001 Vatican statement on xenotransplantation. The statement itself is found under Tab 3 of the conference materials. This recently well-documented statement entitled "Prospect for Xenotransplantation" sets forth the Roman Catholic Church's position on a comprehensive set of philosophical and moral issues that have been and are being discussed in medical, legal and bioethics literature.

Part 1 of the statement consists of a succinct overview of the science of xenotransplantation up through the year 2000. It is very similar to scientific overviews found in the medical literature. Part 1 surveys the four identifiable immunological barriers, experimental animal models, xenoses, PERV, the clinical status of cellular transplants and experimental status of organ xenotransplants.

Part 2 bites the bullet by forthrightly presenting the church's position on a range of philosophical and moral issues that are crucial topics for religious and secular persons alike. These issues include the degrees to which humans can justifiably intervene and manipulate nature or the natural world, the justifiable uses of animals, when xenotransplantation should be limited, how to assess and what to do about health risk and just allocations of medical health care resources. And guidelines for reinitiating, monitoring and publicly discussing clinical trials with whole organ transplants.

The Vatican's statement was drafted by members of the Pontifical Academy of Life and members of the Holy Sea who drew upon the expertise of nine sciences across the world, only one American, and as well as almost all Italian-based moralists, anthropologists, legal experts and others.

The authors of this statement say that it should be regarded as, quote, a useful point of reference for all those who are responsible for leading society. Now, they included as Footnote 74 of the report indicates this SACX committee. They call for debates in public discussion of issues surrounding xeno through the representatives of society such as us in order to identify the conditions under which xenotransplantation can and should be developed.

Now, for those of you who are not well-acquainted with the intellectual foundations for Vatican statements such as this, I will say a word about the scientific, moral and theological foundations of authoritative Roman Catholic pronouncements, intellectual foundations that are reflected in this statement. I should say that as an overview I decided to query several of my colleagues and graduate students about what they think of the church's position would be on xenotransplantation and all but one said, well, obviously the Catholic church would be opposed. To that I replied, well, you've been reading too much of their abortion literature.

So I guess the grain of popular and unformed opinion, the Catholic church does not make pronouncements from on high. They are merely predicated upon dogma and ecclesiastical tradition. Instead, the fact that Part 1 is a straightforward presentation of known facts about the scientific status of xenotransplantation that serves as the basis of discussion for the moral and philosophical issues in Part 2, which constantly appeals to, quote, rational considerations or purely rational analysis and a number of common Democratic values such as human dignity, personal identity, risk and benefits and social justice indicates that this is and similar statements from the Vatican are predicated upon the interplay of three sources of authority: Scientific facts, more reasoning and the church's magisterium, which should be defined as the authoritative theological perspectives drawn from Christian Scripture, notable theologians, councils of bishops and official pronouncements of the papacy. As this point indicates, the magisterium does not assume that it is competent in the experimental sciences. Instead it relies on the tradition of moral reasoning to make judgments about how known, proven and changing scientific facts, discoveries and technologies should be applied.

Now, even a simple survey of Catholic moral reasoning is beyond the scope of this review, but a point or two about this will enable us to identify the complex tradition of moral reasoning upon which this and similar statements rest. Part of this report relies upon moral reasoning that is commonly employed by secular religious ethicists alike, moral codes of action, moral courses of action that rest on foreseeable arms and benefits, respect for human dignity and the autonomy of all persons.

Other parts of this report, especially the first three issues in Part 2, draw upon what is called the natural law tradition of moral reasoning whereby that which is moral is equal in meaning with that which conforms to a rational analysis of the natural world or what the natural world reflects, and within that what the purposes of nature appear to be. This tradition of deriving moral truths off of the face of nature, rational analysis, apart from but at the same time in keeping with the church's authoritative theological teaching began 2000 years ago.

Now, the overarching perspective of the authors of this Vatican statement in contrast to my brief survey of colleagues and graduate students is highly supportive of xenotransplantation research and clinical usage. In its introduction the statement says that xenotransplantation offers the possibility of, quote, relieving the chronic shortage of organs from human donors. On page 4 the statement adds, "Clearly more research in xenotransplantation is needed and should be done." As we shall soon see, none of the ethical and other concerns the statement addresses are viewed as negating what appears to be the great clinical promise of xenotransplanted cells, tissues and organs. Indeed, the analysis of several of these concerns expressly warrant what is termed the urgent need to develop a new xeno as, quote, accepted surgical therapy.

It is notable that the style and contents of this prospects for xenotransplantation document conveys a sense of authority and finality. The issues it deals with are therefore not presented as tentative suggestions or as merely recommendations or as hopefully acceptable perspective but as rational, convincing and true.

The first two topics in Part 2 pertain to the moral and theological legitimacy of utilizing ingenuity and scientific inventiveness to intervene in the natural world, theologically termed in this report the created order, for the good of humankind, humankind embracing the wholeness of every human being. Predicated on a rational understanding of nature that is supplemented by an unabashed and theologically based humanism stemming from the authoritative teachings of the church, this statement holds that we human beings have the right and duty to promote human well-being and dignity. The statement affirms that human beings are, quote, created in the image and likeness of God and therefore have a, quote, unique and higher dignity than all other beings on the Earth. We are placed at the center of the universe and we represent one of the final ends or goals of creation.

From this moral and theological perspective it follows that there is, quote, no substantial problem, page 11, in

utilizing both nonhuman primates and non-primates as cell tissue and organ sources for human beings as long as certain conditions are met. These conditions include preventing unnecessary animal suffering, predicating the use of animals on necessity, human health being one of those, and approving of xenotransplants that will not alter personal identity or the essential core of recipient's ability to both feel that they are human and to be human as they know it and as we know it.

This last point is expanded upon in the third subheading of Part 2 in which certain brain tissue and gonadal xenotransplants are forbidden, but all xenotransplants that are therapeutic or beneficial and do not affect the psychological or genetic identity of persons, subjective identity of persons are permissible.

What about health risks? The statement contains a rather lengthy discussion of health risk that makes a number of sensible suggestions about ways to categorize and calculate various levels of risk related to organ rejection and infectious disease. Very similar to the position taken by the FDA and the subcommittee on xenotransplantation, over time the framers of this statement argue that the absence of data, quote, does not necessarily mean that a total moratorium should be placed on all experimentation.

Instead, I think this is an assumption we've probably had in this committee, or many of us, in the face of unknown risk, xeno research should conform to the ethical requirement of proceeding by small steps with the least possible number of subjects with careful and constant monitoring and with precautions regarding the possibility of quarantine and the requirement of sexual abstinence.

Under informed consent, the longest paragraph on the informed consent in this statement reads like a short version of the PHS guidelines. But beyond these guidelines, the statement holds that, first, because they are unable to give, quote, valid consent, minors should be excluded from experimental xenotransplant research. Second, certain patients incapable of giving consent who are facing imminent death can justifiably depend on proxy consent. And third, research subjects' relatives and contents should be educated but cannot logically give informed consent for, as if in a medical context.

Respecting the allocation of health care resources for xenotransplantation, quite a discussion in the ethic literature, in a straightforward manner this document states on page 15: "The huge amount of health care resources used for xenotransplantation is justified by the urgent need to try to save the lives of so many patients who would otherwise have no choice of survival. This is especially true for xeno in the experimental stages in part because the collective benefits of this research even in the case of allotransplants may outweigh immediate costs."

Under practical guidelines the statement ends with the authors saying that these guidelines, quote, will guide the path of research and development in the future. One of the notable points in this section pertains to the conditions that warrant a resumption of whole organ clinical trials. It will be ethically correct, this statement says, if these trials begin with only a restricted number of patients, namely those who do not have a chance of being chosen as allotransplant recipients and for whom, quote, no better alternative treatment is available.

As you can see, the wording of these guidelines illustrate the point I made earlier about the authoritative language and tone of many of the sections of Part 2 in this notable statement from the Vatican. The authors of this recently published Vatican document rightly conclude at the end of the document that it displays, quote, the close attention which the Catholic Church pays on problems related to human disease and suffering.

I would comment that Pope Leo XII, at least back in the '60s began to make systematic statements on health care issues and served as one of the sort of cutting-edge voices with respect to the right to refuse treatment when one is terminally ill. I will be happy to field questions. My background is not Catholic, but as I said, in the tradition of the academic study of religion, I want to display the tone and content of this report, significant sections of which are very much applicable to some of our own thinking.

DR. GROESCH: Thank you, Harold. In the interest of keeping somewhat on schedule, we are running about 15 minutes behind, and that's cutting into lunch. Is there maybe one question right now?

DR. VANDERPOOL: Thank you.

DR. MENDEZ: No question, I was just highly pleased to see what a positive stance the Vatican took on all of this. It's much more contrary than most of us thought it would be.

DR. VANDERPOOL: Bob, I would have loved to have spent a couple minutes polling the group as I did my colleagues and graduate students, what would you suspect the Catholic Church's position would be on xeno. But by placing humans at the apex of creation and by placing us as part of the purpose and ends of creation, xenotransplantation under those conditions are perfectly acceptable.

I will say that some of this report almost reminds me of a theologian I'm sure most of you spent a good bit of time reading about, although you may never have heard his name, Taillard de Chardin, who is a sort of a mystic evolutionist who sees that the mentation, the mental abilities of human beings is a sign to which the creation is going. And so from that standpoint humans are indeed not only at the apex of creation but at the cutting edge of evolution. Thanks.

DR. GROESCH: Okay. We are running a little bit behind. I would propose that we split the difference a bit and convene at 1:50. That will give us an hour and five minutes for lunch. We'll convene back here. And there is a restaurant that's right down the hall. In addition, as you may have seen when you drove in, there are a number of restaurants nearby in walking distance and also then for the committee members that filled out the prelunch order, there are some tables set aside in the restaurant and your food should be ready. We'll see you back here at 1:50.

(Lunch recess -- 12:47 p.m. to 2:03 p.m.)

DR. VANDERPOOL: Let's begin and we're moving to just the brief statements about the working groups at which point we'll do a session breakout and put Mary Groesch in charge of this session and what we need to do at the breakout periods. Dr. Groesch has points about what we should do as we leave to our separate rooms in terms of what we need to take and what we need to be aware of when we go there.

Agenda Item: Introduction to SACX Working Groups

DR. GROESCH: Okay. The way, we are going to have just a very brief introduction, what are the working groups about, what their charge is, who the members are. And then we'll break one of the -- I made an executive decision that the informed consent working group would meet next door. It's actually a nicer setup for you, there's a table and there are seats there for people who want to listen in on it. The sessions will be transcribed and the state of the science group will be meeting in here. And I think we'll just kind of sit around and elbow at the table there so it will be easier to see one another.

And it would be very helpful if all the members would take their name tents with them because it will help the transcribers, so set yourself up at your new spot and take your materials with you, and then after the break we will meet back in here and hear from both of the working groups what progress they've made to date.

And also we've been requested to remind people to, please, use your microphones whenever you speak, turn it off afterwards and if you see the transcriber waving, that means someone has messed up so, please, use your mikes more religiously. Thank you.

John Allan and Megan Sykes are the co-chairs of the working group on the state of the science in xenotransplantation. And John will just briefly review what the group's charge is.

DR. ALLAN: I'll briefly review what Mary has given me. We don't have these things in Texas.

This is our working group here. Megan and I are co-chairing this group. And as you can see, most of the individuals have some knowledge and expertise in publications in either the science and in, of xeno and in the infectious disease risks. So I think it's probably a good group to start sorting out some of the issues. We've had one teleconference call so far, so we're just getting going. Probably the other group is doing a similar thing. But here's the -- the purpose really is and I'll just read it and you can follow along. A little bouncing ball that runs

across here.

To develop a report or a series of reports described in the current state of scientific knowledge regarding xenotransplantation, to identify critical gaps in our knowledge of the science of xenotransplantation, discuss possible approaches to addressing these gaps -- gasps -- including prioritizing areas for further investigation. We've just started to touch the surface on that.

And to identify and describe the most salient, unresolved scientific, medical, and public health issues in xenotransplantation, including the potential for transmission of infectious agents as a consequence of xenotransplantation, prioritize and discuss possible approaches to addressing these issues. And there was some discussion regarding infectious disease risk as we've had a lot of information on that already and great overview by Jay touching on the major areas that I think need serious attention.

And, but we sort of felt like the area that needed the most attention at this point is the scientific issues in terms of the, getting the xenotransplantation field to move along. So I think that's really where our initial focus is. But we don't want to forget infectious disease risk at the same time. We still have to write our report, so. So I think we've got a lot of work ahead of us. And you want the report next week, is that --

DR. GROESCH: That would be good.

DR. ALLAN: And that's it.

DR. VANDERPOOL: This is about the group, working group on informed consent. Robin wanted me to get up here yet again, I mean, I definitely think your eyes would rest easier on Robyn Shapiro than on me yet again. But I'll do this since this is so brief and Robin wanted me to.

Our working group involves myself and Robin as the co-chairs with Alan, Brad, Cathy, Jim, Sharon, Karen, and Lily as active working members. The mission of our group is to develop a report or a series of reports addressing informed consent issues pertaining to xenotransplantation clinical research, to identify the major topics regarding informed consent in xenotransplantation including emerging and unresolved issues, to identify critical gaps and extant and proposed guidelines and to provide leadership in addressing these gaps and to assess the adequacy of informed consent process employed in xenotransplantation clinical studies, I would say at the present time, and to provide guidance as needed. We had a very successful and exciting teleconference.

And I think we've already, we are already well started on identifying what the issues are. One thing our committee decided was that instead of trying to do an overview of ethical issues as is so often done in the literature, we really ought to get down to brass tacks and focus on one issue. It's probably going to end up being the case that focusing on this one issue will be a very large set of concerns.

We already identified some of the major issues including, first, just defining the essentials of what informed consent involved. Next, dealing with certain process issues concerning informed consent: What is an understandable consent form. To what degree does the length of the form discourage or actually undermine informed consent, and to what degree should informed consent be secured by someone other than the researcher, perhaps a patient advocate, is that a necessary factor. And to what degree is counselling and education needed as mentioned in the guidelines.

Also one of the daunting problems it faces is the number of issues that need to be discussed in informed consent process and the documentation. If we just survey what's in the public health guidelines and what's in the Code of Federal Regulations, we end up with about 20 different topics that need to be addressed. Well, I mean, that makes for a rather lengthy consent form and so we are going to have to figure out what to do with that. Every time we have a speaker or every other time we have a speaker we identify yet another issue on informed consent such as issues involving confidentiality as mentioned today.

Finally, there are very special problems that are quite unique to xenotransplantation. One is the standard clause in all, every informed consent I think I've ever seen on the IRB says that people have a right to withdraw at any time. Well, as drawn up, xenotransplant recipients will not have a right to withdraw but rather will have a

lifelong duty to be monitored, even to the point of autopsy after death. Then there are other knotty issues that, particular issues involving financial liability and so on.

So we have like, as John mentioned the scientific committee, a great deal to accomplish. And I hope that in the short period we have today, we will be able to come back with something that has greater substance than what I've just mentioned. Thanks much.

DR. GROESCH: Okay. So we'll divvy up and people are welcome to come in and out of the groups at any time and these are open meetings. We will be making a transcription of them, so again, take your table tents with you. And also we'll convene back here at 4:20 for plenary discussion of the progress. And you might take a moment or two during your groups and decide if anybody wants to get together tonight. We do have the use of these rooms, so if a group would like to either get together over dinner and continue discussions or come and meet in these rooms, let us know. Okay?

Agenda Item: Breakout sessions for Working Group discussions -- 2:14 to 4:10 p.m. (Transcripts of Working Group meetings provided separately.)

(Recess taken -- 4:10 p.m.to 4:38 p.m.)

Agenda Item: Reports of Working Groups and Plenary Discussion

DR. VANDERPOOL: I want to welcome Cathy Crone with us. She came to our working group on informed consent about an hour or so ago and has made quite an effort to get here and to which we all can be and should be very grateful, thank you, Cathy, for being with us now.

Let's begin with the discussion from the working group on science and safety and then we'll go to the discussion, a report, reporting out on the discussion of the informed consent group.
So, John and Megan.

DR. ALLAN: I think we had a pretty fruitful discussion. We covered as much as we could in the, what was it, two hours or so? What I'm going to do is just sort of give you the five major areas that we initially targeted and then I'll break them down individually. And again, we spent the bulk of our time talking about the sciences of xeno and what areas we need to focus on and the types of speakers we are going to need to bring in in terms, to get enough information to begin to hash out a report.

Potential impact is the first area that we touched upon. I'm not going to go into any great details in our discussion, but essentially what we were talking about is the potential impact on health. And that would be both positive and negative impacts. And let's say if diabetic patients received cellular transplants, what kind of benefit would we achieve. And also negative impacts in terms of on the health care system. And I know Allen Berger had given us sort of an overview earlier in one of our earlier meetings, so we felt sort of that would sort of integrate with some of what Alan had said earlier.

We also discussed alternatives, the potential for alternatives. We didn't go into any detail on that at all, but there was a report by NHLBI that I think included some of the alternatives in that report so we thought that might be helpful. Also the Council of Europe, there was some information there available as a reference that we might target because we are actually thinking about what we need to do to get more information. We need to bring in speakers on all these different topics. And we are trying to limit that as much as we can, so if we can get the information either through already-published reports, we are going to try and do that.

There was some discussion about, there were several other publications on economic impact at Solomon Brothers report that David Cooper said probably was already outdated but that it could be useful. There was another report in terms of the, I think it's called IXLT? ISH -- whatever -- tell us what that is. What is that?

SPEAKER FROM THE AUDIENCE: International Society for Heart and Lung Transplantation.

DR. ALLAN: There you go. So there's that information that we can access as well. And there's also

information on the web that we can get in terms of particular procedures and their effect or their potential impact or benefits on the public health. So we go back to the science of xeno. And this is, again, where we spent most of our time in discussion. And this is Megan's area actually. Here, you start with solid organs. Do you want to work on that?

DR. SYKES: Right. So we went ran some of the major areas related to solid organ transplantation that we haven't covered yet and felt that we needed to bring in some speakers on endothelial cell host interactions, an important area. Another area is species differences in physiologic function, an area that we've already heard a little bit about from some of the speakers who have come in. And it is a relatively small amount but unfortunately there isn't a lot of data out there beyond what we've already heard in part because there aren't people in other areas outside of xenotransplantation who are thinking about this. So the field has really been driven by problems that have already been seen in the existing xenotransplantation field. And since there hasn't really been very long-term graft survival of the solid organs, there hasn't really been an opportunity to see all the potential physiologic incompatibilities that might come up in the future, for example if we have long-term liver xenograft survival. So we decided we probably have heard enough about that and don't need to go into it and can cover it in our report from the information that we have.

The next area was the transgenics, area of transgenics. And we did feel that we needed to hear a lot more about that, particularly on the technology related to porcine ES cells as well as transgenics and to hear about the potential impact on xenotransplantation of the various genetic modifications and also the potential impact on the animals, on their health and viability, and also to hear about the potential infectious disease issues that may come up in relation to these areas. So we have come up with a list of speakers and decided to do our best to hear from a number of different people in order to get as many different points of view as possible because this is such a large and important area.

The next area was cellular transplants, islets, neural cells, myoblasts, hepatocytes. And Dan Salomon is going to cover this for us at our next meeting. It was felt that we might also consider bringing in other species -- I'm sorry, other speakers on other potential donor species.

DR. SALOMON: You know there was a thing, all you need is one talking dog.

DR. SYKES: Finally, our next was extracorporeal technology. There's been a lot of work done in that area, in extracorporeal liver perfusion as well as bioartificial liver devices and we decided that we ought to hear about this, so we'll be bringing in one or two outside speakers in this area and trying to summarize the existing data and come up with a plan for, or not a plan but a, some sort of statement about what we thought the future potential of this approach was.

Then there was systems physiology and what this refers to is systems that apply to all of the above, solid organs, transgenics, cellular transplants, et cetera. Things like complement and coagulation systems, both very important areas that have turned out to be problematic that we really haven't heard about yet so we will bringing in outside speakers. And a third category there was subset of surface molecules that have been identified and recognized, cyalic acid and other differences in carbohydrates that tend to be seen on microorganisms and other species. And we will have a speaker on this area as well.

The next area was immune rejection and tolerance, and this is something that I'm going to have a chance to speak about in the next March meeting. And we'll also bring in an outside speaker to talk about the potential role of immunosuppressive drugs in xenotransplantation. So with that I think we moved to the infectious disease risks and I'll let John come back and tell you about that.

DR. ALLAN: Again, we've spent a lot of time on infectious disease risk. We've heard speakers in the last several meetings talk about infectious disease risks, so we felt we probably had enough information to begin to write a report on the infectious disease risks. And we tried to break it down into several areas. This is an area -- we have spent very little time actually how we are going to structure the infectious disease risk aspects, so I wouldn't even go by what is listed here. But obviously different species have different viral risks and we are going to have to cover those.

There's also, what we put here was the procedural risk, which is there are different risks based on whether it's a cell transplant, whether it's a whole organ transplant, whether it's feeder layers, so we have to deal with, we want to deal with the relative risks of these different types of procedures. And we did spend a few minutes talking about the -- and we are going to hear a talk tomorrow, I don't think it's a talk tomorrow but it's sort of an overview of epicell, which is essentially a skin graft that's been grown on a mouse feeder layer and so the issue arose there about human embryonic stem cells and how do we deal with that issue in terms the fact that it is a xenotransplant, whether we want to get into that, how do you we deal with that, do we fold it into the, or do we talk about it separately, do we bring in somebody to give us an overview of that. And we decided that Bill will talk to -- was it Jim Thompson?

DR. SCHECKLER: Professor Thompson.

DR. ALLAN: Yeah, Professor Thompson, who is actually involved in that area. And we'll get some information, we've had someone from the FDA CBER who is going to provide some information to us tomorrow in terms of where the NIH stem cell research field is. So we'll get a lot more information about that. We are also going to be discussing the science of surveillance and working through that process as well, the surveillance that's required to follow the patient, the public health impact as well.

And then, let's see, we have a couple other things that we haven't even gotten to yet, which is regulations, future prospects. And this is something that we will work on in future meetings and work together with. And the infectious disease risk we'll begin to work with that both through e-mails and through teleconferencing. We are going to break up our working group into a smaller infectious disease group. We are going to start to put a report together. And that's it. What did I miss?

Under the potential impact, we would like to sort of enter a working group situation because of, as I mentioned before, some of the comments that Alan has made prior and the fact that it does touch on ethical issues, we think, we are not sure.

DR. GROESCH: John, we did talk about that it might be useful for people to see the NIH stem cell report and I will just take care of procuring copies of the entire report and get them out to the entire group because I think that would be helpful.

DR. ALLAN: Yes, thanks.

DR. GROESCH: Actually, is there any discussion? I guess we could do discussion of this and then go onto the next group. Did anybody want to comment or ask questions?

DR. VANDERPOOL: I have a question. I'm supposed to present the informed consent group's view. When you had regulations in that fourth or fifth category, did you mean by that that you were going to talk about what you had done earlier with respect, for example, to surveillance and then look at the regulations and see if there are necessary changes to that?

DR. ALLAN: Mm-hmm.

DR. VANDERPOOL: That's excellent. Well, in comparison to the science and safety group we didn't need anyone else in the room, nor did we need anyone else to come help us. I think we had plenty of fire power in that room. And indeed everyone contributed impressively to the issues at play. I think on the issue of informed consent many, if not all, of you science and safety people can also contribute, so perhaps after the discussion we would welcome your comments.

We had Paul, who was taking notes and going to get some things to us so he could continue that process hopefully if those of you on the science and safety working group have comments, but let me just go over what we discussed and then request comments.

The first thing we did was look at a little statement that I put together that would introduce the paper that we have in mind and talk about the theoretical, the values, theoretical foundations for informed consent in a very

straightforward common sensical fashion. What are we talking about when we talk informed consent. And in that little statement we talk about how the phrase informed consent for prospective research subjects seems rather vague and bland but, in fact, is a very powerful protector of human freedom, self-determination, protection from fraud, harm and deceit.

And then there was a brief outline of what consent consists of with its elements of disclosure of information, comprehension or understanding and voluntarism with brief statements about what those are. So that is intended to set up the analysis of the real challenging and difficult, not necessarily difficult but the very challenging and innovative issues that follow.

Now, I don't think you can probably read most of what's there. That happens to be my writing, but I was sort of OCD on jotting things down as the committee went along, and so this captures some of what we talked about. And I'm just going to point out what some of this is.

When we outlined the three constituency guidelines behind informed consent, really the part of what it means, and we mentioned voluntarism, we asked is voluntarism in the case of xenotransplantation undermined by patients' or the subject's desperation. And this could be seen as somewhat similar to very direly ill cancer patients. We didn't really talk about that. We asked the question.

We then shifted to an area in which we talked about what are the unique features of informed consent with respect to xenotransplantation. We said, well, some of the unique features are the public health risks involved which are very different and very important here compared to almost every other protocol, if not all other areas of protocols. The desperation of the patients is very great, will be very great in the first, certainly in the first experimental organ transplant. That long-term follow-up is just entirely unique and calls into play a host of questions we later talked about. For example, if you sign that you will follow up, you consent to be followed, give samples and be monitored all your life, well, can you withdraw from that. Is it possible to withdraw or is surveillance mandatory in the law? It probably isn't, but we have to deal with this issue. You give consent for a long-term follow-up and you decide for whatever reasons not to do it anymore, that is, the phrase and the federal regulations that you can withdraw at any time, have to be jettisoned and say that you can't withdraw any time if you get a xenotransplant procedure. So this is an important issue related to an issue regarding informed consent that is not brought up in almost every other protocol we know of.

Also there's a large number of complex issues that must be disclosed. There are maybe 18 or 20 categories of issues taken from the federal regulations and from the public service guidelines. And this can make for a very long form that depending on how elaborate the detail is could actually serve to undermine consent rather than enhance it. And there may be a battle here between patients consenting to what is going on and lawyers wanting to protect companies and institutions by throwing in details the patients really don't need to hear unless they are particularly scientifically curious.

We worded a little bit over the confidentiality issues that were raised earlier with respect to the database and the specimen, specimen archives, but didn't talk about it at length. We then shifted to talk about whether it's necessary for close contacts and family members to consent. And we talked in and around this to a significant degree and, I think, generally concluded that since these persons would be monitored and since they would have to be part of surveillance and monitoring and have to be willing to control their blood donations or willing to even control sexual activity, that they would need to consent to at least what they were required to do, though they couldn't consent for the procedure obviously. So we generally were moving in the direction this is important. At this point the allotransplant people among us such as Brad Collins, said that, look, in allotransplants, this is from Brad, in allotransplant the family has to buy into the procedure or the patient doesn't get put on the waiting list, or on the list of people to receive the transplant. And so this is a factor in which the family would have to consent.

At play here is the difficult question of is there a certain amount of coercive -- of undue pressure on the family to sign up or the patient won't get anything. If you consent supposedly you are going to do it voluntarily and not under the duress of your family member not getting any procedure unless you consent. But that's a dilemma that we didn't resolve but we certainly recognized that as complex.

When we talk about disclosure, comprehension and voluntarism. We talked about how comprehension is supposed to be -- part of what it means to consent is to find assurances that the patient has comprehended the information. Well, we are lucky to have Jim Finn with us, who spoke very candidly about the degree to which he was presented a 30-page consent form, didn't care about 25 pages of it and just wanted to go ahead with the procedure. And then when he was asked, well, how long did it take, he said it took about six months. So what happened is Jim learned a great deal of things over time. But when he got that chock-full-of-information form he didn't want to hear about that, and so to assure his comprehension of every single dotted I and crossed T on that form would have been almost an egregious form of pressure on Jim. So the question of how much everything on that form has to be comprehended is also an issue. That's the question asked here.

I guess it was Karen who raised the issues about or -- it wasn't Karen it was -- who raised the issue about the mental abilities -- it was Sharon. The mental abilities, not of the doctors, but -- Sharon asked, well, look, I'm concerned about patients with compromised mental ability and can you have substituted judgment for these patients? We talked at some length about that and I think generally agreed that there would be circumstances even when the patient did not expressly hope for an organ or not ever talk about organ transplant, that the subject patient should be able to receive a procedure because the family would deem it, according to Robin's use of the law, in the patient's best interest. So we were somewhat open to the idea that was expressed in the Vatican statement, that those who could not fully consent could have proxy or consent or substituted judgment.

We then went into a very lengthy discussion about who should obtain consent from research subjects. Should it be the researchers. Should it be someone who is not, certainly not a researcher, or both. And we went around and around with that one talking about the pros and what is lost when the researchers don't secure consent and what could be lost if the nonresearcher does all the, quote, consenting.

And we ended up with, I think, an agreement that both parties should be involved in the consent processes with the researcher and physician talking about immune suppression. And later on Lily brought in the importance of quality of life issues, as much as you can describe what the quality of life or way of life will be after the procedure is received. And these types of issues would certainly need to be discussed with patients and finally consented to in terms of signatures on the form, but that someone who was not the physician researcher, a family physician or a social worker but certainly it could be a physician but not someone who is actually doing the procedure, should probably be the one to talk about public health risk, lifelong surveillance and so on. And both of these parties would be able to say that each has disclosed the essential information, comprehension is displayed by the prospective subject and voluntary decision has been made.

Alan made comments about a number of these issues but asked the question about whether there should be a disclosure, financial disclosure of conflicts of interest. Alan may want to elaborate that a little bit more, but he presented this as he's generally in favor of disclosing conflicts of interest in, for xenotransplantation protocols. And so although we did talk about a couple of other matters, at least raised them as things we haven't talked about, I think we covered a great deal of ground and certainly raised issues, Paul said at the end, which was wonderfully comforting, well, look, you don't have to decide what to do with all these ethical issues but you can at least say there's an issue here and one can go either this way or that way and challenge the reading public to think about these issues and both physician and this committee and others to figure out what the best answer would be.

But we don't have to -- I think on informed consent we don't have to figure out everything, but we certainly need to present what the issues are and try to resolve as much as we can. One final comment by way of introduction, what we want to say in this report is that, yes, xenotransplantation is accompanied by a number of ethical concerns and we will list those concerns, but rather than give a sort of cafeteria coverage of these concerns, it's time for the SACX committee to deal in significant detail with the most important of these. And one of the most important of these is informed consent, and there's a great deal to wrestle over with respect to that topic and we are going to take it on.

Now, when you ask questions, I'm not going to field all those. Other members of the committee, please, comment, but I was at least again pressured by Robin to give the overview. Thank you. Ask what questions you will and anyone on the committee feel free to respond. Bill.

DR. SCHECKLER: Thank you. At our community hospital following what the joint commission wants us to do in terms of informed consent, they are very uncomfortable and we are now very uncomfortable having anybody other than the surgeon get the consent from the patient. We frequently in the past had the floor nurse or other proxies do it so that direction for other kinds of procedures, and Brad can probably comment on this too, is to have the person responsible, physician or surgeon responsible for the procedure to get the informed consent and be sure that it happens right.

Second point is that the, one of the things that we've used in primary care for a long time are family meetings where we, in fact, have the physician responsible, perhaps some of the specialists, social worker, nurse, the patient and their family, and we discuss end-of-life issues and other kinds of issues. And this is done with some frequency and when the patient is able to understand and appreciate things it works very well and it would seem to me that that's the same strategy that might be an option for informed consent in something as difficult as xenotransplantation.

And my final point, having served a couple of years ago on the Wisconsin IRB, is the federal regulations are terrible in terms of informed consent. The numbers of things that you are supposed to cover, the level of language that you cover and what the Office of Research Integrity has done to interpreting those have, in fact, made things more complex, more obtuse, made the lawyers perhaps, sorry Robin, made the lawyers perhaps happy, but I don't think they've done much to enhance true informed consent or enhance patient understanding. They've made the informed consent for cancer chemotherapy protocols, for example, terribly long and obtuse just to make sure that we've covered all the points that can make the auditors happy.

DR. VANDERPOOL: And protect the institutions.

DR. SCHECKLER: And protect the institution, but I haven't seen any studies that have suggested that any of this has enhanced informed consent.

DR. VANDERPOOL: Committee members want to comment or reply to what Bill said?

MS. SHAPIRO: We actually talked about that a lot and what a good response to that would be, which is why -- well, to go to your first point. Getting behind the purposes of informed consent, which we see as a process, not a piece of paper, it's to assure that the information that needs to be disclosed is disclosed. And the best person to do that is the person who is going to be doing the procedure, which is why I think most of us felt that first cut should involve discussion between the person who is going to do it or the team that's going to do it and the patient.

But the other purposes of informed consent which are problematic and maybe in most other things have to do with voluntariness and comprehension, so the thought that we followed that conversation up, which wouldn't even necessarily result in yes, Doc, I'll sign on the bottom line, but a conversation to be followed up by another and maybe another where someone else goes in there and says, do you understand this, do you want me to help you ask some more questions, do you want out of this, and can I help you get out of this because you really don't want to go. That kind of thing is a process kind of thing that we were talking about to address your very concerns.

And in terms of the length, we talked about that and we talked about how we could basically get away with meeting the requirements of the law yet making it be meaningful and not meaningless as it seems to have been for Jim.

DR. VANDERPOOL: Other comments? Bob.

DR. MENDEZ: I agree with Robin and also Bill, but in California, again, it is the law that the surgeon must write the consent and get the consent. But we came to the conclusion also that the surgeon doesn't necessarily always give the most comprehensive and best-understood informed consent. And so what we have done is set up a situation in which all patients must mandatorily attend a class, and a class is given by the nurses and social workers, the social caseworkers, and then they see two videos, like videos in which the physicians are also on the video and others that give them all the comprehensive information they can.

After they attend the class they must take a test. It's a six-page test. And then they answer questions, and at the end they must sign their name to that. After that, then they sit with the surgeon, and they go through their consultation. And then the surgeon gives them an informed consent. And he looks over their answers and sees whether or not they are correct or not correct. And it's his responsibility to correct the mistakes or the misunderstandings that they have.

DR. CHAPMAN: What is this for?

DR. MENDEZ: This is for all types of transplantation.

DR. VANDERPOOL: To take the comments of Bill and Bob, in terms of the ethics class that's going on, one of the things that is in the literature is the Institute of Medicine report of 1996 it makes a very forceful set of statements about how in the history of xenotransplantation the surgeons have been overly enthusiastic and optimistic and upbeat and the classic instance of that is the Baby Fae baboon transplant in California, Baby Fae was supposed to end up in college and died about four weeks later. Now, that had been picked up by Nuffield counsel in which surgeons were more or less kept out of the process and even David Cooper -- is David here to defend himself -- takes the point of view that perhaps nonsurgeon researchers should do it.

Now, yours truly wrote -- and part of what Cooper and Lanza are doing is taking me on in an article I wrote in the Lancet in which I said if the surgeon doesn't do this, you lose the meaning of physician-patient relationship which has to be a part of this process because it's going to be so ongoing because there's such a need for trust.

So I think -- I know our committee wrestled with these issues and talked about members of the team making this a very rich communicative process where someone can talk about where are we -- someone can talk about in some detail about the public health risk and really walk people through that level of issues and the surgeons would talk about immunosuppression, quality of life, extension of life and so on.
Other comments? Okay, Dick.

DR. KASLOW: I may have missed it somewhere along the way, Harold, but I wonder if it would be worth your planning to incorporate somewhere along the way in some section or in each of the separate sections a comment or a highlighting in some way of the ways in which you think the xenotransplantation is exceptional or different from other procedures or complex things that people are being asked to consent to.

DR. VANDERPOOL: That's what these points are intended to serve. There are some truly unique features to informed consent in xenotransplantation. And some of those are real conundrums. For example, the issue of lifelong surveillance clashes with the standard statement in every consent form and hopefully every consent process that you may withdraw from this research any time you wish.

Well, I mean, the patient can withdraw before it's ever done, but once it's done, then the patient is, quote, locked in. And you know, that's a different cut. And then the number of issues that form 30-page document raises the question that Jay Katz, one of the profound thinkers in these matters, has said there are such numbing detail that no one knows how to consent to what's going on in this document because it's all just numbing detail and there are no real substantive things a person knows what he or she is consenting to.

But, yes, there are a number of unique issues. And when we get a draft put together -- and by the way, David Cooper did make a very interesting comment we can think about. He said, you know, Harold, I think you all should consider making your position papers as drafts and calling for commentary. So let's -- this would be for all of us, all of our working papers. So we can at least consider that.

MS. KING: This is for Louisa. We discussed in our group the issue of a patient we are saying lifelong surveillance but obviously if someone signs a form, consents to that, but then chooses not to do it after the procedure, what type of recourse exists currently and looking specifically at the public health service. Is there any type of precedent with any like TB patients or, I don't know, of others who are forced to have any type of treatment or follow-up when a public health issue is identified?

DR. CHAPMAN: I can't speak to that legally, but I can tell you things that came up in our discussions when we discussed this internally in PHS working group and through the process of developing the guidelines. In general, in recent years, because it hasn't always been true, but the bedrock principle in human experimentation and consent has been the autonomy of the research subject, which includes in it the right of someone to withdraw. I'm not aware -- well, actually I have seen a presentation by Ed Dolodar (phonetic) at the OECD WHO surveillance meeting in Paris a year ago, this past October, talking about ethical issues, and he did present an example of something called Ulysses contracts. Apparently in the Greek myth Ulysses wanted to listen to the sirens in his boat and so he had his men strap him to the mast and then blind themselves or something so they were -- or stuff their ears so that they were immune to the sirens and they couldn't hear his calls and he made them promise in advance that no matter what he said they wouldn't release him so that he could listen to the sirens and still be protected.

Apparently there are contracts that have been used with people specifically who go in and out of mentally competent states like manic depressives, where when they are in, they are in a rational state of mind, they sign contracts giving them permission for them to be forced to take their medicines when they are no longer in a rational state. I'm not sure that's exactly relevant here because that's addressing an issue where a person is being protected from themselves when they are no longer able to make their own judgments.

In terms of the quarantine laws, quarantine laws were established for and have historically been used in situations where a person by virtue of their presence in the room presents a real and imminent danger to other people of casual contagion: A Typhoid Mary, who by being allowed to work in the kitchen in a restaurant can infect unknowingly people who patronize that restaurant or eat her food. A person with smallpox or typhoid who sitting on a bus with other people simply breathing into the same airspace can affect the people around them.

They have tended to be effective public health tools when you were dealing with infections characterized by casual transmission and a short -- and limited duration of infectivity. They have also been used with active pulmonary TB, which meets the first definition, but where people have a time span held basically incarcerated, although in hospitals for six months to a year. I think the longest period of time now for enforced treatment would be a couple of months until they are noninfected, but if you want to treat them until their, you want to avoid the multi drug resistant thing, you would have to go back to multiple years. I'm not aware that's been used in recent years, and I think in general it has been felt to be a human rights question of whether you have a right to do that.

That sort of thing has been discussed with HIV, which is the closest analogy I'm aware of to this situation in that you are talking about a situation where once you are infected it's a lifelong exposure risk. And furthermore where people are not at risk just by being around you without knowing what you have. They have to have some pretty direct interaction.

It's an imperfect analogy because in an HIV infection person, there's a defined risk, the outcome of that risk is death. And with xenotransplantation recipients we are talking about at present a hypothetical risk that has not been established and never been documented in a patient. In HIV the general -- the only places I'm aware of who have used quarantine laws were, I think Cuba did so, I think China did so, in both instances they were considered international human rights issues and it generally has been considered, I believe, unacceptable from the human rights point of view. From a public health point of view, ignore morality, right or wrong, anything like that from a public health point of view, it simply has not been effective.

DR. SCHECKLER: I have a follow-up on that. Wisconsin has been one of five states working with the Robert Wood Johnson Foundation to come up with model public health statutes because the quarantine laws fundamentally are state laws now and the powers laws for quarantine are state laws. And with the anthrax outbreak there has been some modification of those increasing the powers and trying to have a model law so that the responses and so forth to let's say a smallpox outbreak and trying to contain that smallpox outbreak can be more uniform across the country.

So the whole issue of quarantine, which sort of went away for a long time and used to be part of the public health service and used to be part of Ellis Island and so forth has come back with the anthrax and the threat of

smallpox and some of these other issues, and in fact, in Wisconsin when we did our laws ten years ago, we kept our powers as far as being able to keep somebody with active pulmonary tuberculosis out of circulation even against their will. That was about the only infection that we had.

This is very different than a theoretical risk of a maybe type of infection, which seems to me to be a much softer and less persuasive kind of thing. And I don't know how to answer your dilemma, but there certainly are state laws that allow for certain things, but I can in my more wild imagination think that they could be applicable in this case.

MS. SHAPIRO: I think you are right. I think we are talking about a continuum. Our first worry is not so much we know somebody is out there and is dangerous, but we don't know because they won't do the monitoring. I would think that our group should struggle with this but that going to court to get a court order to enforce that kind of required monitoring wouldn't be an insurmountable challenge.

DR. VANDERPOOL: Other comments from committee members or both on the -- any committee members, but I do want Jim to think about making a statement to the group about your own experiences or something about your experiences. But in the meantime, Dan.

DR. SALOMON: I think this theme of what is unique about xenotransplantation with respect to the informed consent is critical. Because there's a lot of issues with informed consent in general that you don't want to, the committee is not going to solve.

So the situation that I've been sitting here thinking about is in my laboratory I make a xeno cell preparation. And then that, let's say, is pig and may be involved with a feeder cell line and some manipulation thereof and then a surgeon implants it. And informed consent is given and the concept here is that the surgeon is the only one who can give informed consent or is the only one that's necessary to give informed consent. And then, of course, a problem happens, an infectious disease issue, let's say, that's related indirectly either to the use of cellular xeno tissue and/or to the preparation in my laboratory. And we all get sued. And it comes back down to the informed consent. How does this work, then? Is this really one of the defining things about an informed consent in xenotransplantation, because I could see in court someone putting the surgeon up and saying, so what do you know about cellular preparations or gene therapy or endogenous retroviral risks. Where was Salomon, why wasn't he there to comment on it? He's really the culpable one, you are okay, you didn't do anything wrong, and I go down the river.

DR. KASLOW: Up.

DR. VANDERPOOL: Jim, do you have a comment to make? Jim's voice is very powerful.

MR. FINN: I've been through this process myself. I had surgery done five years ago for xenograft put in my brain for Parkinson's disease. When I was in the option of getting involved with this project, I jumped at the chance because I had nothing else to look forward to. My life was coming to an end, I couldn't move, I couldn't walk, I couldn't talk, the whole bit. So when I was approached by the physicians, Diacrin researchers, I was willing to go for it because I just wanted to have something done, I wanted to have a chance to have a better life.

The form they gave me was a 30-page form which you have in your packets. It's very comprehensive, it covers everything, what my responsibilities were, what their responsibilities were, legal things, financial things, and all that. And I don't know what else I can say, I'm glad I did it. It worked very well for me for my Parkinson's symptoms. And I think that's a great potential for xenotransplantation for other diseases and maladies that mankind suffers. I'll take any questions if anybody has any.

DR. VANDERPOOL: Could you mention whether, how interested you were on, about most of the information on those pages.

MR. FINN: I didn't give a damn about the information on the pages, basically. When your back is against the wall like mine was, you jump at any chance for relief from symptoms of whatever disease you might have. I read the informed consent form after I signed, kind of like buying a used car, you don't read the details until you

get it home. And I don't know what else I can say, Harold.

DR. VANDERPOOL: Thank you so much, Jim. Anyone else have a point? Is this the last question, Mary? I just know Mary has a question.

DR. MICHAELS: I'm going to forego the question I had, the comments that I had before and actually just direct this in regard to Jim's comments.

Jim, if you had -- I understand that you were in a situation where you felt desperate and you were willing to sign away anything. You've been very eloquent in telling us that. And it's unfortunate to hear that you didn't get -- that you really read through it in more detail afterwards. Do you think that the classes or meetings or sessions beforehand might have been helpful so that something we could structure differently to help other individuals that might be in this position?

MR. FINN: I think a patient advocate would have been very good to sort of guide me through the decision-making process. I was kind of on my own with this. But on the other hand, this is one of the first xenotransplantations ever done, so I was on the cutting edge of this and there was no patient advocate, there was no thoughts of that kind of thing. As I said to our group meeting, I have contacted Diacrin and said hire me as a patient advocate, I'll promote your product, you know, but so far I'm still not employed by Diacrin.

DR. VANDERPOOL: Thanks for that question, Marian, and for the response from Jim.

I think it's time to disband. Oh, that's right. Public comments. Sorry.

DR. GROESCH: Nobody had requested in advance that they wanted to make a comment, but please, everybody here has heard the discussions. If you would like to comment on anything you've heard recently or anything today or anything that you wanted to add, we would very much like to hear it.

MS. KING: I have a request. I don't know if the gentleman is here who earlier today had information on what was happening internationally.

DR. GROESCH: Robin Pierson, he's not here anymore, he had to leave.

MS. KING: As a committee, I would love to hear more information about that in the future. I know we talked about that in the past, but I would still be very interested in that.

DR. GROESCH: Okay.

Agenda Item: Closing Remarks

DR. VANDERPOOL: There are other issues that have been raised. The question that Dan Salomon raised about the difference between serious adverse events and adverse events and other things. There are a variety of issues that we raised but didn't cover today, but we certainly covered a great deal.

And is it all right, Mary, to say we are now adjourned until 8:30 tomorrow morning? Let's be sure to start on time with the FDA overviews and plenary session discussion. It should be very exciting.

(Whereupon, open session ended at 5:35 p.m.)